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ETIOLOGY OF ULCERATIVE COLITIS

I. THE PREPARATION, CARE AND SECRETIONS OF COLONIC EXPLANTS IN DOGS

ROLF LIUM, M.D.

AND

JOSEPH PORTER, M.D.

BOSTON

In an endeavor to investigate the cause of ulcerative colitis, colonic explants were chosen as the most suitable preparation for study of the reactions of the colon under direct vision. The method of preparing such explants was first described by Drury, Florey and Florey.[1] These investigators included no detailed account of the care given the explants except to say that dressings were applied. They reported that the surface of the explants was redder than that of the normal colon because of contact with the air and with the dressings. Raiford and Eberhard [2] used a similar preparation, but without protective dressings [3] and reported changes in the surface structures of the explants resembling those due to chronic inflammation. It is our purpose in the present paper to show that with careful attention the explant can be maintained indefinitely in what appears to be a normal condition so far as its gross as well as its microscopic appearance is concerned. As a part of this study, quantitative measurements of the secretion of the explants were made.

METHODS

Fifteen medium-sized dogs were used in these and subsequent experiments.[4] With the animal under pentobarbital sodium anesthesia (intravenous), a section approximately 3 cm. in length was resected from the midportion of the colon.

From the Surgical Research Laboratory, the Fifth Surgical Service (Harvard), and the Mallory Institute of Pathology, of the Boston City Hospital.

1. Drury, A. N.; Florey, H., and Florey, M. E.: The Vascular Reactions of the Colonic Mucosa of the Dog to Fright, J. Physiol **68**:173, 1929.

2. Raiford, T. S., and Eberhard, T.: Pathological Changes in Exteriorized Gastro-Intestinal Grafts, Ann. Surg. **104**:175, 1936.

3. Raiford, T. S., and Eberhard, T.: Personal communication to the authors.

4. Lium, R.: Etiology of Ulcerative Colitis: II. Effect of Induced Muscular Spasm on Colonic Explants in Dogs, with Comment on Relation of Muscular Spasm to Ulcerative Colitis, Arch. Int. Med., this issue, p. 210.

An end to end anastomosis was done by the Parker-Kerr technic. The resected segment was then brought outside with the mesenteric pedicle intact. The layers of the abdominal wall were sutured loosely around this pedicle, and a section of skin, the size and the shape of the graft, was then excised. The segment of colon was opened along its antimesenteric border and sewed to the edges of the area of excised skin. The edges of the explants were usually firmly healed and adherent to the cutaneous incision at the end of ten days. Figure 1 shows the appearance of the preparation in dog 4 after healing was complete.

For 7 animals (dogs 1 to 7) a quantitative study was made of the secretion of mucus by the normal graft according to the following technic. Clean dressings were dried in an oven at 45 C. for twenty-four hours and accurately weighed. They were immediately applied to the graft and twenty-four hours later were removed and weighed at once. The dressings, with the adherent secretion, were dried again at 45 C. for twenty-four hours and again weighed. The figures gave the amount of solid plus moisture secreted by the graft and the amount of total

Fig. 1.—The appearance of a graft twenty days after preparation. The photograph also shows the adhesive binder used to hold the dressings in place.

dry solids, respectively. The error due to evaporation was reduced to a minimum by the use of absorbent dressings which were covered by a heavy adhesive binder of double thickness.

With this method the daily amount of mucus secreted was determined during control periods of normal feeding. The effect of changes in the character of the stools was noted during such periods, and subsequently the effect of starvation and of dehydration due to vomiting and diarrhea was observed. The effect on the amount of secretion of leaving the dressings in place for two days instead of changing them daily was determined. Finally the progressive changes in the explant were observed when the dressings were left off for one month.

RESULTS

Severe spasm was present in the musculature of the graft during the twenty-four hours immediately after its preparation. It was noted that ulcers appeared in the central portion of the preparation, where no

trauma had been inflicted. After this initial period the muscular spasm disappeared, the ulcers healed and the grafts, which were treated by daily dressings, looked perfectly normal for long periods. Figure 2 is a photomicrograph of the mucosa from a graft in dog 6 which had been prepared eight months previously. In figure 3 is shown for comparison a microscopic section of normal colonic mucous membrane from dog 8. Careful study of these two preparations showed no appreciable difference.

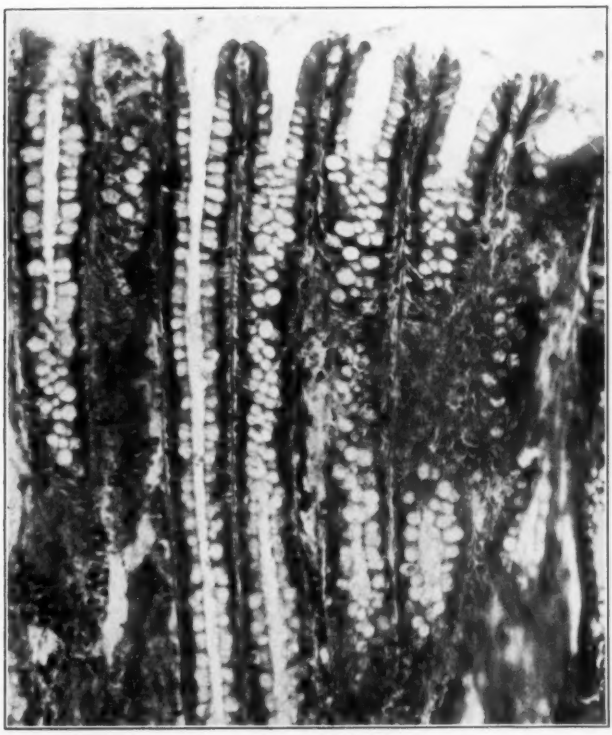

Fig. 2.—Photomicrograph (× 200) of a normal, resting graft eight months after preparation.

During the period of healing, which was from ten to fourteen days on the average, there was at first a thin, watery secretion of mucus. This gradually changed during the first ten days after operation to the typical thick mucus which was found in a layer on the dressing whenever the latter was removed.

The application of a dressing to a normal graft invariably caused an immediate visible increase in muscular tone and a prompt secretion of

mucus. In twenty-four hours a layer approximately 2 mm. thick and exactly equal to the size of the graft was found. There was also some moisture diffused throughout the dressing. Table 1 shows the amount of mucus and solids secreted daily by dog 11 over a twelve day period of normal feeding. Whether the stools were hard or soft appeared not to influence significantly the daily amount of secretion. In all 7 animals similar results were found during such control periods. No constant

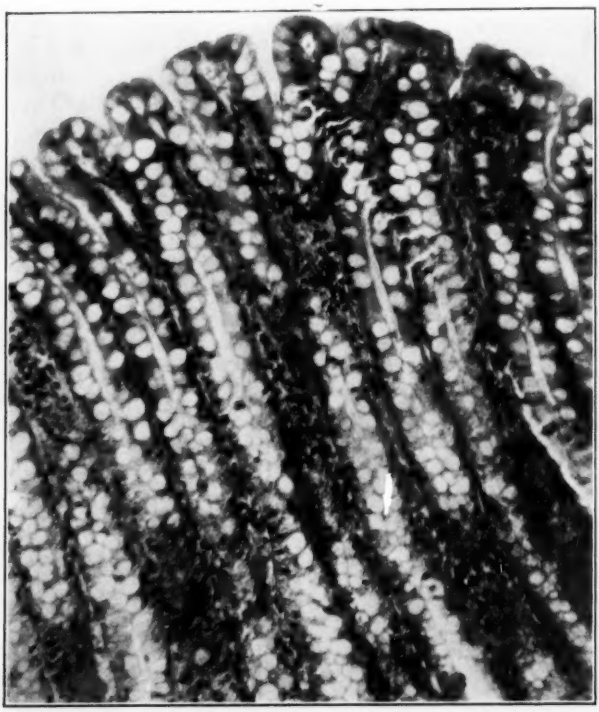

Fig. 3.—Section (× 200) of normal colon taken from a dog at death.

relation could be established between the amount of secretion and the surface area of different grafts.

In each of 3 other animals (dogs 7 to 9) that were starved for a period of four days, the secretion of mucus by the graft was not measurably diminished as compared with the secretion during the control period of normal feeding. Table 2 shows for comparison the values for these animals during four day periods of feeding and starvation. Three other animals (dogs 10, 13 and 14) evidenced no measurable change in the total amount of secretion on the dressing when it was left in place for

forty-eight hours instead of being removed every twenty-four hours, as was done during the preceding control period. The results are shown in table 3.

TABLE 1.—*Daily Amount of Mucus Secreted by the Colonic Graft in Dog 11 Over a Period of Twelve Consecutive Days*

Date	Weight of Secretion, Gm.		Type of Stool
	Mucus	Solids	
4/3	2.86	0.25	Formed; hard
4	2.75	0.19	Formed; soft
5	2.54	0.40	Formed; soft
6	2.09	0.30	Loose
7	4.33	0.36	Formed; hard
8	2.91	0.34	None
9	3.19	0.34	Formed; soft
10	3.08	0.29	Formed; soft
11	2.39	0.33	Formed; soft
12	3.05	0.43	Diarrhea
13	4.34	0.37	Formed; soft
14	3.76	0.32	Hard; small pieces

TABLE 2.—*Daily Amount of Mucus and Solids Secreted During Alternate Four Day Periods of Starvation and Feeding*

Dog No.	Diet	Date	Weight of Secretion, Gm.			
			Mucus		Solids	
			Daily	Total	Daily	Total
7	Starved	5/16	3.71		0.47	
		17	3.65		0.35	
		18	3.50		0.52	
		19	2.96		0.59	
				13.82		1.93
	Meat and milk	20	2.90		0.45	
		21	3.73		0.56	
		22	3.69		0.57	
		23	3.26		0.50	
				13.58		2.08
8	Starved	5/19	2.80		0.62	
		20	3.18		0.63	
		21	3.26		0.54	
		22	2.04		0.46	
				11.28		2.25
	Meat and milk	23	2.99		0.54	
		24	2.03		0.65	
		25	1.91		0.10	
		26	2.87		0.39	
				9.80		1.68
9	Starved	5/19	2.48		0.68	
		20	3.26		0.64	
		21	2.07		0.50	
		22	1.93		0.45	
				9.74		2.27
	Meat and milk	23	2.25		0.41	
		24	1.43		0.16	
		25	1.68		0.42	
		26	1.74		0.49	
				7.10		1.48

Two of the animals (dogs 5 and 6) suffered from marked dehydration. Dog 5 had intractable vomiting, and dog 6 suffered from almost continuous diarrhea. Table 4 shows the marked diminution in the weight

of the secretion on the dressings of both explants during these periods. The dry solids, which were measured only for dog 5, were diminished proportionately with the total secretion.

TABLE 3.—*Weight of Mucus and Solids Secreted When Dressings Were Changed Daily Compared with Weight When Dressings Were Left in Place for Two Days*

Dog No.	Date	Number of Days	Weight of Secretion, Gm.	
			Mucus	Solids
10	5/24	1	2.99	0.54
	25	1	2.03	0.04
	26	1	1.91	0.10
	27	1	2.87	0.27
	29	2	2.90	0.28
13	5/22	1	3.73	0.57
	23	1	3.69	0.50
	24	1	3.26	0.50
	26	2	3.19	0.46
14	5/24	1	2.25	0.41
	25	1	1.43	0.16
	26	1	1.68	0.30
	27	1	1.74	0.31
	29	2	1.87	0.31

TABLE 4.—*The Amount of Mucus Secreted During Periods of Normal Nutrition and Periods of Dehydration*

Dog. No.	Condition	Date	Weight of Secretion, Gm.	
			Mucus	Solids
5	Meat and milk	3/20	2.53	0.31
		21	2.18	0.22
		22	2.47	0.13
		23	5.00	0.22
		24	3.52	0.20
Average			3.14	0.21
	Vomiting	3/31	1.03	0.02
		4/ 1	1.20	0.09
		2	1.28	0.06
		3	1.61	0.10
		4	1.24	0.05
Average			1.27	0.06
6	Meat and milk	3/ 1	4.05	
		2	3.75	
		3	3.90	
		4	3.80	
		5	3.14	
Average			3.72	
	Diarrhea	3/ 6	1.73	
		7	0.21	
		8	0.92	
		9	1.07	
		10	1.50	
Average			1.08	

In order to determine why in the experiments of Raiford and Eberhard pathologic changes were noted in the explants, 2 animals (dogs 12 and 13) were allowed to go without protective dressings over the explant for a period of one month, when microscopic sections were made. Dur-

ing this period the dogs licked their grafts frequently, and shavings and sawdust from the cage would rub across the surfaces. Within one day after the dressing was abandoned these explants lost their rugae and showed flattened surfaces. Their gross appearance was distinctly that of chronic inflammation, and after three days small ulcers were noted on the surfaces. Figure 4 is a photomicrograph of a section from such

Fig. 4.—Photomicrograph (× 200) of a section of mucosa from a colonic graft exposed without a dressing for one month. Note the marked inflammatory reaction, the absence of mucus and the loss of the normal deep glands.

a preparation (dog 12) taken thirty days after the beginning of exposure. There are a marked inflammatory reaction in the submucous tissues and a layer of fibrin with inflammatory cells on the surface. This particular section was made through the edge of an ulcer which is seen in the photomicrograph. Only an occasional goblet cell can be seen. Sections taken thirty days after the beginning of exposure of the graft (animal 13) were similar.

COMMENT

So long as colonic explants are covered with dressings they appear normal and cannot be differentiated microscopically from normal colon. These findings are in agreement with those of Drury, Florey and Florey.[1] Prolonged exposure of two grafts without dressings demonstrated that the similar chronic inflammatory changes noted in such explants by Raiford and Eberhard were probably due to the absence of protective dressings. None of our protected grafts showed pathologic changes, and grafts which had been uncovered for a week healed promptly on resumption of regular dressings.

The amount of mucus secreted in twenty-four hours was relatively constant for a given graft. The consistency of the amounts of this secretion during the control periods and periods of starvation suggests that the initial mechanical stimulation due to the application of the dressing is largely responsible for the amount of secretion that is formed. This is further substantiated by the finding that the amount of secretion on the dressing was the same whether the dressing was changed after twenty-four or after forty-eight hours. The conclusion of Florey [5] that the secretion of mucus by the explants is a response to superficial mechanical irritation is thus confirmed. Once the mechanical irritation of the dressing has been removed by the interposition of a layer of mucus between it and the graft, secretion of mucus apparently stops. The physiologic importance of the mucus in protecting the normal colon from superficial mechanical irritation is thus suggested.

That superficial irritation is the sole cause of secretion of mucus by the colon as an intact organ or is indeed the proximate cause of secretion of mucus is, however, not a necessary conclusion from the present observations, nor is this conception substantiated by the work of Larson and Bargen.[6] These investigators carried out extensive observations on the secretion of mucus by an isolated loop of dog colon. Because fecal material did not traverse the loop, local mechanical irritation was absent in their experiments; yet secretion of mucus was appreciably increased at the time of defecation and whenever cathartics were administered. In the present studies it was noted that whenever a fresh dressing was applied, muscular contraction, together with an outpouring of mucus, took place in the graft. No significant variations were noted in our experiments with respect to whether the stools were formed or solid. Indeed, there was remarkable constancy of secretion, regardless of whether the animal was fed or starved. It may well be that the irritation caused by the dressing was such a dominant factor in determining

5. Florey, H. W.: The Secretion of Mucus by the Colon, Brit. J. Exper. Path. **11**:348, 1930.

6. Larson, L. M., and Bargen, J. A.: Action of Cathartics on Isolated Dog's Colon: Secretory Activity, Arch. Surg. **27**:1120 (Dec.) 1933.

the amount of secretion by the method used that increases in the amount of secretion associated with muscular activity due to the defecation reflex were overshadowed.

In later experiments, reported elsewhere in detail,[4] it was found that the resting explant of colon secreted a thick layer of mucus whenever it was stimulated to muscular activity by various means. Mucus is thus apparently secreted whenever natural or artificially induced muscular activity takes place and is apparently expressed from the goblet cells by the action of the underlying muscles.

CONCLUSIONS

The colonic explant in dogs prepared by the method of Drury, Florey and Florey represents normal bowel wall so long as it is continually protected with dressings.

The secretion of mucus by such grafts when dressed each day is remarkably constant and is little influenced by the digestion of food or by starvation. Dehydration, on the other hand, markedly diminishes the amount of secretion.

Secretion of mucus by the colonic explant appears to be largely a response to the initial mechanical stimulation of the dressing, which is associated with muscular contraction. The layer of mucus once formed on the dressing protects the graft from further stimulation.

The dominant effect of irritation caused by the dressing in inducing muscular contraction and secretion of mucus probably explains our failure to observe increases in secretion brought about by normal reflex muscular activity, as noted by Larson and Bargen.

Dr. S. Maddock supplied the animals and the facilities for conducting these experiments. Dr. W. B. Castle advised with us concerning the preparation of the manuscript. Dr. C. K. Drinker made available the facilities for preparing the photomicrographs.

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ETIOLOGY OF ULCERATIVE COLITIS

II. EFFECT OF INDUCED MUSCULAR SPASM ON COLONIC EXPLANTS IN DOGS, WITH COMMENT ON RELATION OF MUSCULAR SPASM TO ULCERATIVE COLITIS

ROLF LIUM, M.D.
BOSTON

In the preceding article [1] a method was described of preparing colonic explants in dogs and of quantitating the secretion of mucus by such explants. On the days immediately after the preparation of the explants, ulcers were found near the center of the grafts. A feature constantly associated with this phenomenon was marked muscular spasm of the explants. When dressings were continuously used the initial muscular spasm disappeared, the ulcers healed and the grafts retained indefinitely a normal gross and microscopic appearance. Thereafter, mucus was secreted largely in response to the initial mechanical stimulation of the dressings, and this secretion was associated with muscular contraction.

It was noted that chronic surface irritation produced by leaving the grafts without dressings for forty-eight hours led to muscular spasm and an initial copious outpouring of mucus. This was soon replaced by a more watery secretion, at a time when microscopic study of the mucosa showed that the goblet cells contained no mucus. The explants showed edema, ulceration and other signs of chronic inflammation. These observations suggested that it might be worth while to study further the effect of severe muscular spasm of the explant when induced by various means. It was hoped thereby to determine the factors underlying the development of pathologic states in the preparation and to discover from their sequence a possible relation to ulcerative colitis.

EXPERIMENTS

Explants of the colon were prepared and protected, according to the method already described, in 15 dogs. These animals were given daily a routine diet of meat and milk.

From the Surgical Research Laboratory and the Fifth Surgical Service (Harvard) of the Boston City Hospital.

1. Lium, R., and Porter, J.: Etiology of Ulcerative Colitis: I. The Preparation, Care and Secretions of Colonic Explants in Dogs, Arch. Int. Med., this issue, p. 201.

1. EFFECT OF MUSCULAR CONTRACTION PRODUCED BY MECHANICAL STIMULI

Stimulation of the graft was made in separate experiments on 9 dogs by wiping with gauze, by pinching with a hemostat and by exposure without a dressing for forty-eight hours. In order to estimate the muscular activity of the explant after stimulation, the longitudinal and transverse diameters passing through the center of the explant were measured at intervals of a minute for five minutes before the experiments commenced and at frequent intervals thereafter. Once the experiment was begun, the number of measurements taken depended somewhat on the activity of the muscles. It was assumed that the transverse diameter was an indication of the function of the circular fibers and that the longitudinal diameter was an indication of the function of the longitudinal muscle fibers.

In 5 cases (dogs 1 to 5) control measurements were taken daily for two weeks. Immediately after each control period the graft was wiped with an ordinary gauze sponge from right to left in line with the circular muscle fibers. It is obviously impossible to quantitate such a stimulus accurately; hence only two grades of pressure were used—heavy and light. When the graft was stroked once lightly with gauze, only mucus came away, and the graft showed some contraction. There was no evidence of significant trauma. If a second light stroke was applied immediately after the first, a little mucus was wiped away, and the graft showed fine bleeding points on its surface. When a single heavy stroke was made over the surface of the resting graft, mucus was wiped off the surface, and the graft bled at once and contracted more forcibly and longer than when a light stimulus was used. The duration of the contractions that followed such stimulation varied in the same graft from time to time and in different grafts, but it was always true that the heavy stimulus produced a greater response than the light stimulus. The changes in the size of the graft in dog 2 that resulted from light and heavy stimulation on different days are given in table 1. After a heavy stimulus with gauze the hemorrhage from the surface was markedly increased by the severe muscular contractions that developed, and large amounts of thick mucus mixed with blood were poured onto the surface.

Three grafts (in dogs 3 to 5) were pinched with an ordinary hemostat in three places after control measurement of the graft. Only the mucosa was included in the bite of the snap, which was removed immediately after the trauma had been inflicted. This led to severe spastic contraction of such marked degree that the graft felt like a mass of cartilage. At times the graft relaxed slightly, only to resume its severe contractions. Immediately after the pinching, a large amount of mucus was poured out on the surface. Not only was there bleeding from the points damaged by the snap, but petechial hemorrhages appeared beneath the mucosal surface in the areas that had not been pinched. At times these areas bled into the mucous coat on the surface of the graft.

The contractions lasted for one-half hour and gradually ceased during the ninety minute period of observation; at the end of this time, however, the graft had not reached its original size. The graft had returned to its usual size on the day after the pinching, and in four days, dressings being applied, the traumatized areas were completely healed. The following protocol gives the data for one of these experiments:

Dog 4.—*The effect of pinching the mucosa of the explant in three places with a hemostat.*

2:24: The graft was in excellent condition. No evidence of surface irritation was seen. The graft measured 4.7 by 3.7 cm.

3:55 p. m.: A Kelly clamp was applied to the mucous membrane in three places. The size of the graft immediately afterward was 4.4 by 3.3 cm.

4:03 p. m.: The graft measured 4 by 3.7 cm.

4:05 p. m.: The graft measured 4.2 by 3.8 cm. It was hard, and the mucous membrane was piled up into wide rugae.

Table 1.—*The Effect on the Dimensions of the Explant (3.6 by 3.4 Cm.) in Dog 2 from Light and from Heavy Stimulation with Gauze* *

	Light Stimulation		Heavy Stimulation	
	Length, Cm.	Width, Cm.	Length, Cm.	Width, Cm.
Immediately	2.7 3.0 3.3	3.4 3.5 3.5	2.5 2.5	2.5 2.9
1 minute	3.5	3.5	3.0 3.1 3.1	2.9 2.9 3.1
2 minutes	3.5	3.4	3.1 3.2 3.2 3.3	3.3 3.2 3.3 3.5
3 minutes	3.5	3.4	3.3 3.4	3.5 3.3
4 minutes	3.5	3.4	3.5 3.5	3.3 3.3
5 minutes	3.5	3.4	3.5	3.3

* During a control period of five minutes measurements were made at one minute intervals. No change was noted.

4:11 p. m.: The graft measured 4 by 3 cm. It had a stony hard surface. It bled freely from the surface, and there was a liberal coating of mucus.

4:20 p. m.: The graft measured 4 by 3.5 cm. It showed petechial hemorrhages beneath the mucosa in places other than those pinched. Some of these had ruptured onto the surface. The mucosal surface appeared inflamed; it was edematous and was covered with a ⅛ inch (0.3 cm.) layer of mucus.

4:30 p. m.: The graft measured 4.3 by 3.5 cm.

5:00 p. m.: The graft measured 4.3 by 3.5 cm. It was inflamed and showed considerable oozing from the surface of blood and thin, watery secretion. A dressing was applied.

2/25: The graft felt soft. The mucous membrane between the pinched areas appeared normal, and the damaged places were healing.

2/28: The graft was completely healed. There was no evidence of the damaged places.

In 4 animals (dogs 7, 8, 9 and 12), after suitable measurement of the control dimensions of the graft, the dressings were removed for forty-eight hours. The preparations were thus exposed to surface irritation from licking and contact with the débris in the cage. The change in the appearance and the size of the grafts and the daily secretion of mucus were all carefully studied. In one series of experiments biopsies were made of all four explants forty-eight hours after removal of the dressings. In another series of similar experiments the amount

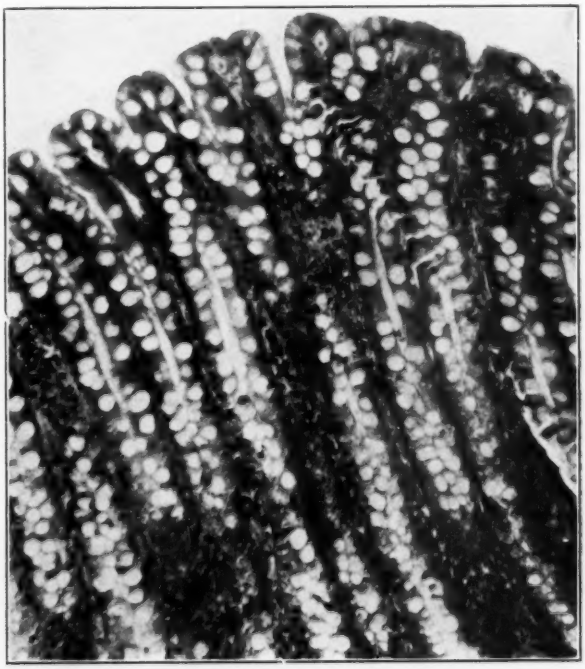

Fig. 1.—Photomicrograph of a normal, resting graft; × 200.

of mucus secreted was weighed by the method described in the preceding article.[1]

After exposure for forty-eight hours the graft became red and indurated and lost its normal rugae. The surface either was almost flat or was thrown into wide folds that were three times the width of normal rugae. Microscopically the grafts showed complete absence of goblet cells, fibrin appeared on the surface, loss of surface continuity was noted in certain places and evidences of inflammation were seen in the mucosa. Figure 1 is a photomicrograph of a normal colonic

explant which had been protected with dressings. Figure 2 shows an explant forty-eight hours after removal of the dressing. In all 4 animals the grafts decreased in length. In 3 the width remained essentially the same as before exposure, but in dog 12 the width increased slightly. Table 2 gives the actual measurements for this series of animals. The results were essentially the same in all 4 animals.

At the end of the forty-eight hour period of exposure, dressings were reapplied and changed daily. The layer of mucus that was

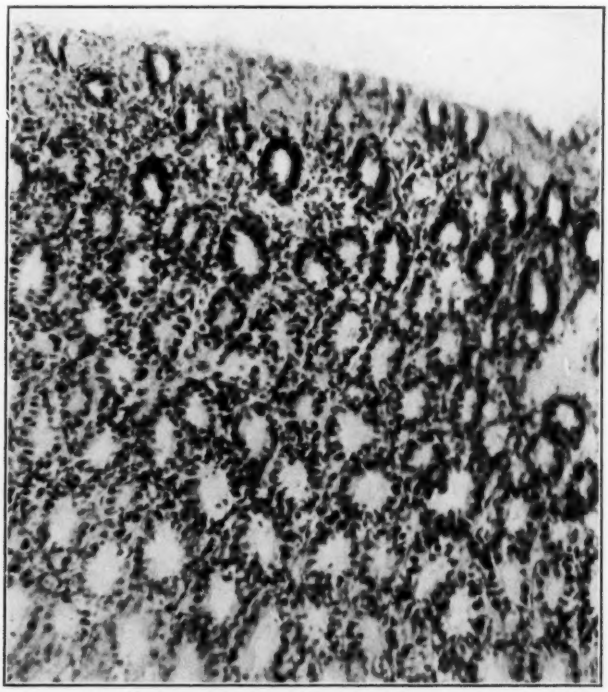

Fig. 2.—Photomicrograph (× 200) of a graft forty-eight hours after exposure without dressings. Note the absence of goblet cells, the increased cellular reaction and the loss of surface continuity.

secreted during the first twenty-four hours after exposure was much thinner than that normally laid down. The film of mucus could scarcely be seen on the gauze, whereas normally it was a glistening layer about 2 mm. thick. The dressing was saturated with moisture, indicating a serous type of secretion. The increase in the dry weight of the material secreted on the dressings was not proportionate to the increase in the liquid weight, showing that the secreted material con-

tained more water and less solids than the mucoid secretion formed by the normal graft. Table 3 gives the daily amounts secreted by dog 7 in two experiments and by dog 12 in one experiment.

TABLE 2.—*The Effect of Exposure to Surface Irritation on the Size of the Colonic Explant*

Dog No.	Average Dimensions of Explant Before Exposure, Cm.		Average Dimensions of Explant After Exposure, Cm.	
	Length	Width	Length	Width
7	3.8	3.6	3.1	3.5
8	5.8	4.7	5.0	4.7
9	5.4	4.4	4.4	4.1
12	4.4	3.3	3.9	3.7

TABLE 3.—*Effect of Exposure Without Dressings for Forty-Eight Hours on the Subsequent Amount of Secretion by the Colonic Graft*

Date	Weight of Mucus, Gm.	Weight of Solids, Gm.
Dog 7: First experiment		
Control		
4/18	5.63	0.18
4/19	5.58	0.47
4/20	5.31	0.40
4/21	4.76	0.55
After 2 days of exposure without dressings		
4/24	21.13	0.24
4/25	10.43	0.51
4/26	5.00	0.39
4/27	5.47	0.65
Dog 7: Second experiment		
Control		
4/28	5.57	0.22
4/29	5.72	0.32
4/30	4.92	0.30
5/ 1	3.91	0.33
After 2 days of exposure without dressings		
5/ 4	13.83	0.15
5/ 5	15.61	0.38
5/ 6	8.47	0.74
5/ 7	4.75	0.32
Dog 12: First experiment		
Control		
5/ 1	6.18	0.25
5/ 2	5.50	0.39
5/ 3	5.80	0.54
5/ 4	4.90	Not done
After 2 days of exposure without dressings		
5/ 7	19.28	0.47
5/ 8	11.71	0.35
5/ 9	5.56	0.33
5/10	4.34	0.32

When daily dressings were resumed, the amount of mucus of the normal, thick variety increased rapidly, and within seventy-two hours a good layer was found on the dressings, with only the usual slight amount of moisture diffused throughout. It is of interest that 2 animals

(dogs 7 and 9) scratched their grafts and so produced ulcers, which were not covered with mucus until healing had occurred. After dressings had been reapplied for one or two days, the mucosal surface of the explants appeared normal except for any ulcerations that had formed. However, all the explants which had been protected for twenty-four to forty-eight hours bled much more readily when stroked lightly with gauze than those which had been at rest and protected for several weeks. It seemed as if the regenerating epithelium were much more sensitive to trauma than that of the normal, resting explant.

2. EFFECT OF MUSCULAR CONTRACTION PRODUCED BY ACETYLCHOLINE AND PROSTIGMINE

From the work of Dale and Dudley [2] it has been established that acetylcholine is parasympatheticomimetic in its action. Prostigmine enhances this activity by inhibiting the esterase which normally hydrolyzes acetylcholine in the tissues.[3] In order to produce maximum muscular activity in the explant, these two agents were combined. One-half cubic centimeter of 1:4,000 solution of prostigmine was given intravenously, and immediately thereafter at five minute intervals for forty minutes 0.2 cc. of a 1 per cent solution of an acetylcholine salt was applied on the surface of the graft.

In all 6 animals (dogs 9, 11 to 15) the grafts contracted violently immediately after the acetylcholine was applied and remained in a state of almost constant spastic contraction during the application of this agent. Within fifteen minutes every explant showed petechial hemorrhages, which gradually increased in size and coalesced. In the dogs which showed a maximum response, the surface at the end of an hour appeared like a piece of raw beef. There was a rich secretion of thick mucus during the early part of the experiment, but this gradually changed to a thin, watery secretion. On the day after the experiment the grafts still appeared somewhat inflamed, and small flecks of blood were found in the mucous coating. After forty-eight hours the grafts again looked normal. The following protocols give the data for the experiments on dogs 14 and 15:

Dog 14.—*The results of experiments with acetylcholine and prostigmine.*

6/12/37; 4:45 p. m.: Prostigmine (1 cc.; 1:4,000) was given intravenously. Acetylcholine chloride was placed on the surface of the graft. Every five minutes during the next forty minutes, 0.2 cc. of a 1 per cent solution was applied.

4:50 p. m.: A violent spasm of the graft was followed by blanching, and the graft turned pale yellow. On relaxing, it became pink, but immediately afterward a contraction of two minutes' duration set in.

4:52 p. m.: The graft was beginning to appear swollen, and small petechiae were visible beneath the surface of the epithelium. There was a generous secretion of thick mucus on the surface. Alternate contraction and relaxation occurred, but the graft did not relax to its original size.

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2. Dale, H. H., and Dudley, H. W.: The Presence of Histamine and Acetyl Choline in the Spleen of the Ox and the Horse, J. Physiol. **68**:97, 1929.

3. Loewi, O., and Navratil, E.: Ueber humorale uebertragbarkeit der Herznervenwirkung, Arch. f. d. ges. Physiol. **214**:678, 1926. Aeschlimann, J. A., and Reinert, M.: Pharmacological Action of Some Analogues of Physostigmine, J. Pharmacol. & Exper. Therap. **43**:413, 1931.

4:58 p. m.: Hemorrhages were appearing on the surface.

5:52 p. m.: Up to this time the graft had been in a state of spastic contraction most of the time, with short periods of partial relaxation. The surface appeared raw, it oozed blood and it was swollen and edematous. The secretion had changed from a thick to a thin, watery mucus.

Dog 15.—*The results of experiments with acetylcholine and prostigmine.*

6/13/37; 10:33 a. m.: Solution of prostigmine (1 cc.; 1:4,000) was given intravenously. One per cent solution of acetylcholine bromide was applied every five minutes to the surface in doses of 0.2 cc. during the next forty-five minutes.

10:35 a. m.: There was a severe spasm, with blanching of the surface.

10:36 a. m.: Petechial hemorrhages were beginning to appear on the surface. With contraction of the surface, the graft blanched. On relaxation there was immediate flushing of the graft. The spasm of the muscles, both circular and longitudinal, in this case was sustained.

10:45 a. m.: The graft was beginning to appear swollen and edematous, and multiple hemorrhages were seen. A tremendous amount of thick mucus had been secreted

10:52 a. m.: A ⅛ inch (0.3 cm.) layer of thick mucus was removed with forceps, care being taken not to touch the graft. Many hemorrhagic streaks were seen in the mucus. The graft looked as though it had been pounded.

11:25 a. m.: A biopsy specimen was taken. Thin mucus had been secreted for the past fifteen minutes. The graft was bloody on the surface.

At the end of the period of application of acetylcholine, biopsy specimens of the grafts were taken for all 6 animals. A photomicrograph of the mucosa from the explant in dog 14 is shown in figure 3. When compared with the normal explant (fig. 1) the outstanding features were distention of the subepithelial vessels, with rupture in some places and bleeding onto the surface of the mucosa; absence of mucus from the cells, and loss of surface continuity of the epithelial cells in a number of places, with the formation of small erosions.

3. EFFECT OF MUSCULAR CONTRACTION PRODUCED BY SHIGA DYSENTERY TOXIN

It has been shown by Reid, Anderson, Stubblefield and Ivy [4] that Shiga dysentery toxin produces severe enteritis when given intravenously to dogs and that the colon is most severely affected. Ecker and his associates [5] noted that the intravenous injection of Shiga toxin and

4. Reid, P. E.; Anderson, M. X.; Stubblefield, H. I., and Ivy, A. C.: Protective Action of Sodium Thiocyanate Against Dysentery Toxin (Shiga), J. Infect. Dis. **55**:112, 1934.

5. Ecker, E. E., and Biskind, M. S.: The Effect of Certain Toxic Substances in Bacterial Cultures on the Intestinal Movement: II. Effect of Filtrates of Young Cultures of the Colon-Typhoid Group of Organisms on the Intestinal Movement of Rabbits as Recorded by a New Cinematographic Method; Correlation of This Effect with the Production of Food Poisoning by Members of This Group, Arch. Path. **7**:204 (Feb.) 1929. Ecker, E. E., and Wolpaw, B. J.: The Effect of Certain Toxic Substances in Bacterial Cultures on the Intestinal Movement: IV. The Production and Action of the Toxic Substances of Bacillus Dysenteriae (Shiga-Kruse), ibid. **10**:407 (Sept.) 1930.

of filtrates from young cultures of Bacillus paratyphosus B caused increased tone or an increase in amplitude of contraction or both in the exteriorized intestine of rabbits. Experiments were undertaken to observe the effect of Shiga dysentery toxin on the colonic explant and to determine whether the damage produced might not be due to spasm of the muscles.

Accordingly, Shiga toxin was prepared from a four day broth culture by the method of Reid, Anderson, Stubblefield and Ivy.[4] Six animals (dogs 1 to 6), which had been used in the study of normal secretion of mucus, were employed in these experiments.

In the first group of experiments with dogs 1 to 3, toxin (filtrate A) was used from an organism which failed to grow on subculture. One cubic centimeter of filtrate was placed on the surface of each graft thirty minutes before each intravenous injection. There was no visible response of the graft after such an application. The filtrate was then given intravenously in doses beginning with 0.25 cc. per kilogram of body weight, and the injections were continued thereafter, 0.5 cc. per kilogram being given. In dogs 1 and 2 daily injections of toxin were given for five days. Dog 3 received injections every four days for five doses.

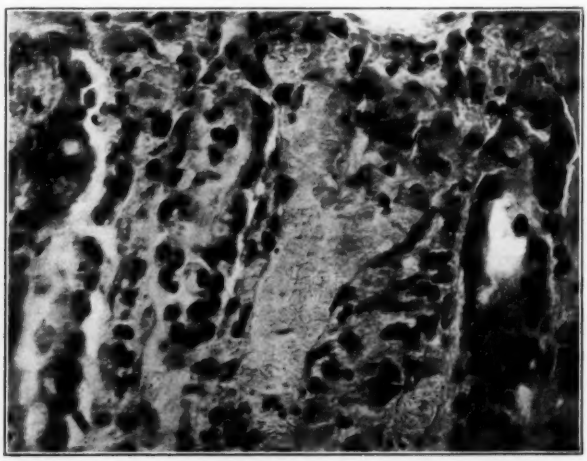

Fig. 3.—Photomicrograph (× 400) of a graft fifty-five minutes after the administration of prostigmine and acetylcholine chloride. Note the absence of mucus, the distention of the vessels and the loss of surface continuity. One capillary can be seen emptying directly onto the surface of the graft.

Dogs 1 and 3 showed the typical effect of intravenous injection—vomiting, diarrhea and bloody stools. About fifteen seconds after the toxin had been injected into these animals, powerful spastic contractions developed in both the circular and the longitudinal fibers of the grafts. At brief intervals during the next twenty minutes the violent activity of the muscles was punctuated by slight relaxation. After this

the activity gradually subsided, and the graft was at rest an hour after the injection. Associated with the spasm was the appearance of edema and induration. Petechial hemorrhages were seen on the surface of the explant from five to seven minutes after the injection, and in twenty minutes much fresh blood was oozing from the graft. At first, thick mucus was secreted in abundance, but later this changed to a thin, watery secretion. On the day following an injection of toxin, the graft appeared red, hyperemic and edematous and showed punctate ulcers which had bled into the mucus on the dressing.

For dog 3 the injections were made several days apart, and for dog 1 injections were given daily. The effect was the same in these animals. Each successive injection led to severe spasm and a more rapid appearance of hemorrhage from the surface of the graft than at the previous injection. In dog 1 the graft returned to normal four days after the final injection, but in dog 3 nine days elapsed before the mucosal surface approached normal. The protocol on a series of injections given to dog 3 was as follows:

Dog 3.—*Intravenous administration of Shiga dysentery toxin.*

2/19; 4:53 p. m.: Shiga toxin (5 cc.) was given intravenously.

4:55 p. m.: Considerable spasm of the graft was noted.

4:59 p. m.: The graft relaxed occasionally but was contracted most of the time.

5:00 p. m.: Petechial hemorrhages began to appear on the surface.

5:15 p. m.: The graft was alternately relaxing and contracting, the contractile phase taking up three fourths of the time. There was considerable oozing of blood on the surface. The dog was having diarrhea with tenesmus. Small specks of blood were in the stools.

2/20: The graft was dressed and was found to be red and edematous. There were numerous petechial hemorrhages in the mucous covering. The dog had diarrhea, with bloody stools.

2/21: The dog had tarry stools, followed by tenesmus, during which drops of bright red blood appeared. The graft was in much better condition. Only a few hemorrhagic areas remained.

2/22: The graft was improving, being almost normal. The dog had loose stools, with old blood on the outside of the feces. Bright red blood appeared, with tenesmus at the end of defecation.

2/23: The graft appeared normal. Proctoscopic examination revealed a red, edematous mucous membrane with considerable hemorrhagic ooze from the surface. Several small ulcers were seen.

2:15 p. m.: Shiga toxin (5 cc.) was given intravenously. The graft became spastic at once, and petechial hemorrhages appeared in three minutes.

4:15 p. m.: The dog had had loose, bloody stools, with much tenesmus, during the past one and one-half hours. The graft showed many hemorrhagic areas. The spasm had gradually relaxed.

2/25: Proctoscopic examination revealed a markedly inflamed mucous membrane which bled easily. A few small ulcers were seen.

2/28: The graft appeared normal.

8:48 p. m.: Shiga toxin (5 cc.) was given intravenously.

8:50 p. m.: The graft showed spastic contraction of marked degree.

8:51 p. m.: There was considerable hemorrhagic ooze from the surface of the graft. The dog was having severe tenesmus, with bloody dejecta.

Concomitant with the changes in the graft were diarrhea, tenesmus and vomiting. When the administration of the toxin had been omitted for several days, the consistency of stools gradually returned to normal, but blood showed on the surface. At the end of the movement the dog continued to strain and would produce several drops of bright red blood and mucus. This observation was made for both dog 1 and dog 3 on five successive days. It seemed as if the act of defecation set up enough spasm in the irritated bowel to produce the bloody mucus at the end of the movement. Proctoscopic examination of dogs 1 and 3 forty-eight hours after the injection of toxin revealed an inflamed, edematous mucosa, which bled freely when wiped with gauze. Small ulcerations were seen throughout the entire segment of colon examined (12 cm.).

In the third animal (dog 2), which received filtrate A daily, no spasm of the graft was seen, and there was only mild diarrhea, without blood in the stools. This animal, however, vomited continuously and had formed tarry stools, which showed a strongly positive reaction to tests for occult blood. Proctoscopic examination after the fifth injection of toxin revealed no abnormality in the colonic mucous membrane of this animal. It was able to retain no food and only small amounts of fluid; it died ten days after the final injection. At autopsy, several large ulcers were observed in the duodenum and jejunum which were the probable source of the occult blood in the stools. Both the colon and the explant were normal on gross and microscopic examination.

The second group of experiments was performed on 3 other animals (dogs 4 to 6), filtrate from another Shiga organism being used. Both four (filtrate B) and ten (filtrate C) day cultures were used. Filtrate B was given to dogs 4 to 6 in initial doses of 0.5 cc. per kilogram of body weight; when this produced no effect, the dose was increased gradually up to 2 cc. per kilogram. Only transient diarrhea resulted. There were no bloody stools, and the grafts did not show any increased muscular activity. Filtrate C was given, with similar results. Another Shiga strain was not available, so further experiments could not be conducted. Biopsy material was not obtained, because the last experiments were unsuccessful.

4. EFFECT OF ISCHEMIA WITHOUT MUSCULAR CONTRACTION

Because of the possible action of muscular contraction in causing the lesions just described through secondary disturbances of circulation, experiments were conducted in which local ischemia without muscular

spasm was produced. As has been shown by Drury and his associates,[6] the colonic explant blanches when the animal is under light ether narcosis. Three animals (dogs 4 to 6) were therefore given light ether anesthesia for a period of forty minutes in order to permit observation of the effect of ischemia on the explant. Although the blanching was pronounced and the muscles were relaxed, there appeared no edema, hemorrhage or secretion of mucus on the surface. Solution of posterior pituitary double U. S. P. strength was given intravenously to the same animals in 0.5 cc. doses. Marked blanching of the graft without muscular contractions was noted. The blanching was present intermittently over a period of one-half hour. Again no surface changes were observed.

COMMENT

The findings in these experiments may well help to explain some of the clinical facts about ulcerative colitis. When severe spasm of the colonic explants was induced by mechanical irritation, by parasympatheticomimetic drugs or by Shiga toxin, a markedly injurious effect on the mucosal surface resulted. An initial outpouring of mucus was followed by secretion of a more serous fluid at a time when the goblet cells of the mucosa were found to be empty. Hyperemia and hemorrhages into the mucosa were commonly observed, and ulcerations appeared in many instances. Over the area of these ulcers no mucus was secreted until healing had occurred. Even after apparent healing, the mucosa was more sensitive to trauma than normally. That these deleterious effects were not produced by ischemia secondary to muscular contraction is suggested by negative results of ischemia without muscular contraction produced by light ether narcosis and by solution of posterior pituitary.

If spasm is a prime factor in the causation of ulcerative colitis, one would expect to find pathologic changes in those parts of the colon with the most powerful musculature. The strongest muscles of the colon are in the rectum;[7] and elsewhere the strength of the tenial bands exceeds that of the circular fibers.[8] In 95 per cent of the patients with ulcerative colitis the disease commences in the rectum.[9] Its further

6. Drury, A. N.; Florey, H., and Florey, M. E.: Vascular Reactions of the Colonic Mucosa of the Dog to Fright, J. Physiol. **68**:173, 1929.

7. Kirkes, W. S.: Handbook of Physiology, ed. 16, Philadelphia, P. Blakiston's Son & Co., 1900.

8. Gleize-Rambal, L.: Sur l'individualité anatomique du côlon descendant, Compt. rend. Soc. de biol. **99**:2015, 1928; **100**:368, 1929.

9. Rankin, F. W.; Bargen, J. A., and Buie, L. A.: The Colon, Rectum and Anus, Philadelphia, W. B. Saunders Company, 1935.

development along the course of the most powerful muscles was well described by Virchow:[10]

> In particular it is the projections of the mucous membrane, caused by the anatomical distribution of the muscle tissue, which are affected by preference. Hence the especial susceptibility of the mucosa along the insertion of the three longitudinal muscle bands and of the transverse folds of the membrane.

In the last 2 patients with ulcerative colitis whom I have studied post mortem, the mucous membrane of the rectum was entirely denuded, and there were three streaks of denuded surface along the descending colon and sigmoid flexure. These lay directly over the tenial bands. There were other minute ulcerations appearing between the tenias. Their linear arrangement, corresponding to the direction of the circular muscle fibers, was striking.

That muscular spasm may lead to erosion of the mucosal surface of all portions of the intestinal tract, including the colon, is suggested by the observations of Light, Bishop and Kendall.[11] These investigators produced acute gastric ulcers in rabbits by placing pilocarpine hydrochloride in the subarachnoid space. In 7 cases the stomach was observed directly. It contracted severely as soon as the drug was given and continued its intermittent spastic contractions for two hours. Although these authors attributed the changes primarily to ischemia and secondarily to digestive action of the gastric juices, the observations made in the present investigation suggest that spasm was the primary factor in producing the results.

In further support of the importance of muscular spasm in the production of ulcers in the intestinal tract was the appearance of duodenal and jejunal ulcers in 1 of the animals (dog 2) that was given potent dysentery toxin. In this animal the ulcers may well have been produced by spasm of the upper portion of the intestine, just as the ulcerations in the graft and colon of dogs 1 and 3 were the result of muscular hyperactivity.

Admittedly, in all patients with ulcerative colitis the process does not commence in the rectum, and some have areas of so-called focal colitis elsewhere in the large bowel.[11a] In such cases it is possible that localized spasm has developed in one section of the colon without involvement elsewhere. Supportive evidence for this contention is

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10. Virchow, cited by Flexner, S., and Sweet, J. E.: The Pathogenesis of Experimental Colitis and the Relation of Colitis in Animals and Man, J. Exper. Med. **8**:14, 1906.

11. Light, R. U.; Bishop, C. C., and Kendall, L. G.: The Response of the Rabbit to Pilocarpine Administered into the Cerebrospinal Fluid, J. Pharmacol. & Exper. Therap. **47**:37, 1933.

11a. Lium, R., and Porter, J. E.: The Distribution of Lesions in Ulcerative Colitis and Its Possible Significance, Am. J. Path., to be published.

found in the appearance of ulcerative lesions in the colon above an obstruction. For example, in 1 patient who had carcinoma of the rectosigmoid region, the muscles were hypertrophied and contracted immediately above this lesion, and the mucous membrane overlying them was almost completely denuded. Below the obstruction, however, the mucous membrane was normal. It seems reasonable to suppose that spasm of the muscles would occur above but not below the obstruction and so may have determined the location of the ulcerations in the mucous membrane.

In considering certain well known clinical features of ulcerative colitis, further evidence is found suggesting that muscular spasm may play a role in initiating the process. At least early in the disease, the shortened, narrow colon commonly seen on roentgen examination is due to spasm, for Rankin, Bargen and Buie [9] have presented evidence that such a "pipe stem" colon can be returned to normal by medical treatment. Patients with this disease are usually high strung and react with excessive sensitivity to their environment. It is common knowledge that nervousness will produce diarrhea, and this may well develop to the point where the colon is in an almost constant state of spasm.

An original attack of bacillary dysentery has been found by several authors to precede the development of ulcerative colitis.[12] Recently Felsen [13] has argued strongly for bacillary dysentery as a frequent precursor of ulcerative colitis. The observations of Ecker and his associates [5] and the experiences reported in this paper show that the intravenous injection of Shiga toxin produces violent muscular contractions. Although other authors have postulated a specific injurious effect of the dysentery toxin on the mucosal cells, it has been shown in the present investigation that the severe injury resulting from intravenous injection of toxin was entirely similar to the result obtained when muscular spasm was produced by mechanical irritation or by the use of parasympatheticomimetic drugs. That the toxin does not act as a specific poison to the epithelial cells was well shown by the negative response of the mucosal surface to direct application of the toxin.

If, then, the colon is an organ which can produce much self injury simply by its own overactivity, once this mechanism is set in motion, the experiments reported here further suggest how a vicious cycle of pathologic changes may become established. The normal protective action of mucus was plainly shown by the fact that after twenty-four hours, when a layer of mucus had formed on the surgical dressing,

12. Hurst, A. F.: Ulcerative Colitis, Excluding Tropical Diseases, Lancet **1**:636, 1931. Thorlakson, P. H. T.: Ulcerative Colitis, Canad. M. A. J. **19**:656, 1928.

13. Felsen, J.: Relationship of Bacillary Dysentery to Distal Ileitis, Chronic Ulcerative Colitis and Nonspecific Intestinal Granuloma, Ann. Int. Med. **10**:645, 1936.

no further secretion of mucus occurred. During the early stages of induced muscular hypermotility in the explants, a layer of thick mucus was secreted, but this gradually changed to a thin, watery type of secretion. Microscopic sections showed complete absence of goblet cells in the mucous membrane. That the fecal stream may well injure the epithelial cells once the secretion of mucus becomes deficient is shown by the observations on the effect of mechanical stimulation on the explant. A light wipe with gauze removed the film of mucus from the surface without causing bleeding, while a similar wipe applied immediately afterward caused bleeding from the mucosa.

Presumably, when the intact colon is stimulated to hyperactivity, the supply of mucus becomes exhausted, and the epithelial cells are no longer protected from the irritation of the passing fecal stream. Moreover, in the present experiments it was noted that when ulcers formed, mucus was not secreted by the ulcerated areas until healing had occurred. Even after return to a normal appearance, the regenerated colonic epithelium was found to be far more susceptible to mechanical injury than normal epithelium. Such observations indicate elements which further contribute to the chronicity of pathologic processes in the colon after the initial injurious effect of muscular spasm.

It is possible that a deficiency of mucus might be the primary factor in certain cases of ulcerative colitis. Tilden and Miller [14] produced ulcerations in the colon of monkeys with a diet deficient in vitamin A. Other investigators [15] have shown that vitamin A is essential for the normal function of mucus-secreting cells in the gastrointestinal tract. That such deficiency of mucus encourages ulcer formation is also demonstrated by experiments with menthol.[16] This substance depletes the store of glycuronic acid, which is a necessary substance for the production of mucus. When the depletion is complete, ulcerations and inflammatory reaction are found along the gastrointestinal tract.

Degenerative lesions of the mucosa of the gastrointestinal tract have been found in diseases in which deficiency of some portion of the vitamin B complex is suspected—pernicious anemia, pellagra and sprue.[17] Similar deficiencies have been demonstrated in instances of chronic ulcerative

14. Tilden, E. B., and Miller, E. G., Jr.: Response of the Monkey to Withdrawal of Vitamin A from the Diet, J. Nutrition **3**:121, 1930.

15. Richards, M. B.: Role of Vitamin A in Nutrition, Brit. M. J. **1**:99, 1935. Cramer, W., and Kingsbury, A. N.: Local and General Defense Against Infections, and the Effect on Them of Vitamin Deficiency, Brit. J. Exper. Path. **5**:128, 1924.

16. Manville, I. A.: The Interrelationship of Vitamin A and Glycuronic Acid in Mucine Metabolism, Science **85**:44, 1937.

17. Mackie, T. T., and Pound, R. E.: Changes in the Gastro-Intestinal Tract in Deficiency States, with Special Reference to the Small Intestine: Roentgenologic and Clinical Study of Forty Cases, J. A. M. A. **104**:613 (Feb. 23) 1935.

colitis;[18] and although usually regarded as secondary to the intestinal disturbances, they could certainly contribute to the chronicity of the process. Thus several factors, all of which are effective in initiating damage to colonic mucosa, may begin the vicious cycle of spasm, mucus exhaustion, damage to the surface structures and further spasm which is essential to the production of the final picture of ulcerative colitis.

SUMMARY

Colonic explants in dogs react to various stimuli by a spastic contraction of the musculature. Whether this spasm is produced by mechanical stimulation, parasympatheticomimetic drugs or dysentery toxin, its result is damage to the overlying epithelial structures, with hemorrhage and ulceration.

The mode of action of dysentery toxin in producing ulcerations of the mucosa is thus apparently through the injurious effects of muscular spasm.

Secretion of mucus is immediately increased in association with muscular contraction of the explant. When hyperactivity of the muscles continues, only a thin, watery material, inadequate for protective purposes, is secreted.

Ulcers are not covered with a coating of mucus until they have healed; thus, presumably, in the intact colon they are constantly exposed to trauma from the passing fecal current.

Even after a return to a normal gross appearance, the regenerating epithelium is more sensitive to trauma than normal epithelium of the colonic graft.

Ulcerative colitis may be conceived as a specific reaction to a number of influences which can initiate spasm of the colonic musculature. These include possible hyperactivity of the parasympathetic nervous system, infections such as dysentery, and vitamin deficiency. Once the colon becomes spastic, it is potentially an organ that can produce severe damage to its own surface structures. The exhaustion of the secretion of mucus, together with nutritional deficiency, may contribute to prevent healing of the colon. That muscular spasm may be responsible for lesions of the mucosa of other portions of the gastrointestinal tract is suggested by certain of the present experiments as well as by a reinterpretation of the work of others.

Dr. S. Maddock furnished the animals and materials used in these experiments. Dr. W. B. Castle gave advice regarding the preparation of the manuscript. Facilities for the making of the photomicrographs were made available by Dr. C. K. Drinker. The preparation of the sections used in these studies and their interpretation were the work of Dr. J. Porter, of the Mallory Institute of Pathology.

18. Mackie, T. T.: Ulcerative Colitis: II. The Factor of Deficiency States, J. A. M. A. **104**:175 (Jan. 19) 1935.

ABNORMALITIES OF CALCIUM METABOLISM

FLETCHER B. TAYLOR, M.D.

PAUL MICHAEL, M.D.

AND

LEONARD BARNARD, M.D.

OAKLAND, CALIF.

Faulty calcium metabolism accounts for a wide range of discomforts and disabilities and in some of its forms leads to untimely death. There have been enough interest and effort on the part of chemists, research workers and clinicians to improve the efficiency of the treatment of patients with this disorder.

Calcium is deservedly a central figure in mineral metabolism. Americans ingest too little calcium salt. The body does not naturally conserve calcium. In fact, if there is a shortage in the supply of calcium or if there is an increased demand for it, e. g., during pregnancy, excretion proceeds without economy, and the organism is confronted with progressive deficiency.

Oversupply of calcium is probably never a practical problem in human beings. In those persons with abnormal deposits of calcium salt, the problem is one of perversion of distribution and not one of excessive intake.

A series of experiences in the field of calcium metabolism has prompted this report. The following case records, presenting a variety of clinical patterns, may help to clarify some phases of the subject.

REPORT OF CASES

CASE 1.—*Calcinosis universalis.*

The patient, a man aged 20, was well until July 1927, when fever developed and there was soreness in all the accessible muscles. Some of the muscles became swollen and there was marked limitation of articular motion because of the swelling and soreness. He became drowsy and passed an excessive amount of urine. In this uncomfortable state he entered the Alameda County Hospital where he was thought to have rheumatic fever. He was given salicylates. He was not much improved when discharged to his home.

A year later he reentered the hospital with the same symptoms plus contractures of the joints of the arms and legs. In 1929 two years after the onset, a nodule developed on the medial side of the left knee joint, and a few months later another one developed symmetrically over the right knee joint. Biopsy showed that one of these contained calcified inflammatory tissue (fig. 1). Similar nodules developed at various points, including the elbows, the flexor surface of one meta-

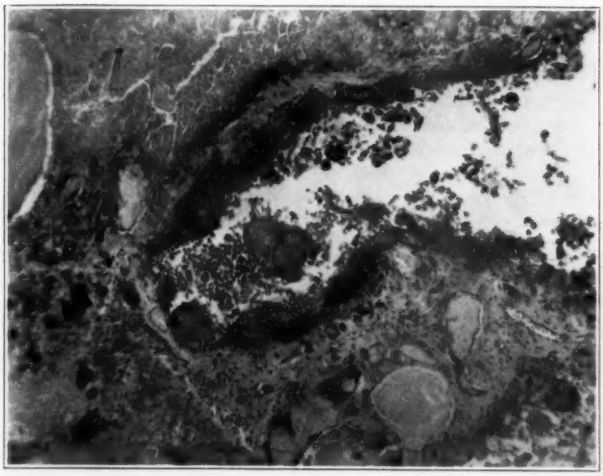

Fig. 1 (case 1).—Calcinosis universalis. Microscopic section of a biopsy specimen from a nodule on the knee joint. Note the hyalinization of stroma, with areas of foreign body reaction manifested by giant cells, macrophages and fibroblasts. The homogeneous small and large masses are calcium phosphate.

Fig. 2 (case 1).—A roentgenogram of the ankle and heel, showing demineralization of the bone, with increased trabeculation. Note the deposition of calcium in the achilles tendon.

carpal bone, the medial side of the right humerus and both heels. These nodules were palpable, and roentgenograms showed infiltration with calcium (figs. 2 and 3).

With the passage of time there was increased calcification. Treatment was symptomatic. A ketogenic diet, which made the p_H of the urine 5.2, may have caused a slight remission of symptoms.

This patient was studied extensively at the University of California Hospital and at the Cowell Memorial Hospital as well as at the Alameda County Hospital. He weighed only 115 pounds (52 Kg.). His height was approximately 5 feet and 9 inches (175 cm.). Emaciation was marked. His blood pressure was 120 systolic and 80 diastolic. Other physical findings were not significant. The complete blood count was normal. The quantities and ratio of albumin and globulin in the serum were normal. Studies of the total calcium balance showed nothing abnormal. The carbon dioxide-combining power of the blood plasma was 61.5 volumes per cent. The p_H of the blood was 7.5.

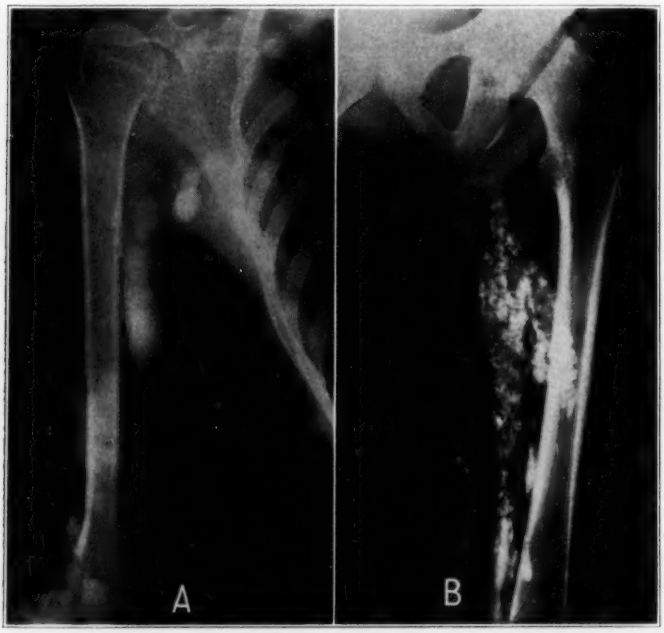

Fig. 3 (case 1).—*A*, the shoulder girdle and humerus, showing some patchy demineralization, with scattered depositions of calcium in the soft tissue. *B*, the lower portion of the pelvis and femur, showing patchy demineralization, with massive calcification in the muscles of the thigh.

Comment.—The normal quantities of calcium and phosphorus in the serum, the normally available carbon dioxide and the moderate increase in the alkalinity of the blood were probably not concerned with this

picture of abnormal deposition of calcium. Oscar Klotz [1] considered this condition in 1905. He explained that a poor blood supply and lessened viability of the cells result in the formation of a succession of alkali soaps, with final deposition of calcium soap.

Scleroderma is often associated with calcinosis, and the histologic changes in the skin in cases of scleroderma have been shown by Epstein [2] to be stages in a process of calcification. Langmead [3] has shown that in cases of myositis fibrosa and dermatomyositis also suggestively similar pathologic pictures are presented.

The late Dr. Campbell Howard [4] said he believed that thyroid therapy helped 2 of his patients with scleroderma. We tried a ketogenic diet, thinking to mobilize calcium from its abnormal sites, as in the case reported by Kennedy,[5] but without clinical benefit. There is no treatment which is dependably successful.[6] Flooding the patient with sodium biphosphate has sometimes been beneficial.[7] A deposit of calcium about the joints is sometimes removed by hyperemia induced by heat.[8] Even normal bone becomes rarefied if it is made hyperemic.[9] Acidosis and local hyperemia may help in the resolution of early calcium deposits in some cases.

CASES 2 AND 3.—*Renal rickets.*

Two patients with renal rickets were studied in the laboratory of the Children's Hospital of the East Bay. No single patient available to us presented all the characteristic findings of this disease but a composite picture of these 2 patients is informative. The term rickets is misleading, because renal rickets is not a vitamin deficiency disease. Renal rickets is the result of nephritis with poor excretion of phosphates.

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1. Klotz, O.: Studies upon Calcareous Degeneration, J. Exper. Med. **7**: 633, 1905.

2. Epstein, N. N.: Calcification of the Skin and Subcutaneous Tissues, Arch. Dermat. & Syph. **28**:510 (Oct.) 1933.

3. Langmead, F. S.: The Relationship Between Certain Rare Diseases, Arch. Pediat. **40**:112 (Feb.) 1923.

4. Howard, C. P.: Personal communication to the authors.

5. Kennedy, R. L. J.: Calcinosis and Scleroderma: Treatment of a Case by Use of the Ketogenic Diet, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W. B. Saunders Company, 1933, vol. 24, p. 1087.

6. Rothstein, J. L., and Walt, S.: Calcinosis Universalis and Calcinosis Circumscripta in Infancy and Childhood, Am. J. Dis. Child. **52**:368 (Aug.) 1936.

7. Craig, J., and Lyall, A.: A Case of Calcinosis Universalis and a Suggested Method of Treatment, Brit. J. Child. Dis. **28**:29 (Jan.-March) 1931.

8. Hitchcock, H. H.: Calcium Deposits About Joints, West. J. Surg. **45**:353 (July) 1937.

9. Orton, G. H.: Calcium Changes and Their Importance in Diagnostic Radiology (Mackenzie Davidson Memorial Lecture), Brit. J. Radiol. **9**:102 (Feb.) 1936.

The first patient was a girl of 6 years who had always been smaller than normal. She was in fair health until a few weeks before her terminal illness. Then she suddenly had a convulsion and after that had excess urine, headache, nausea and vomiting. She had hypertension (130 systolic and 90 diastolic) two weeks before her death. This blood pressure reading was fairly representative of the period of acute illness. The urine contained large amounts of albumin. Only 10 per cent of the phenolsulfonphthalein injected intramuscularly was excreted in the urine in two hours. The nonprotein nitrogen content of the blood was 150 mg. per hundred cubic centimeters just prior to her death in uremia.

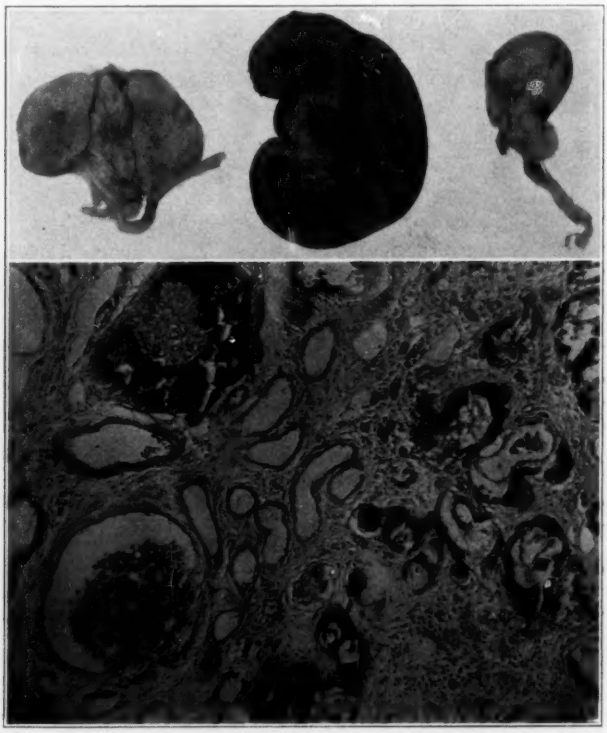

Fig. 4 (case 2).—Renal rickets. Necropsy specimens of the kidneys and a normal kidney from a child of the same age for comparison. Note the marked hypoplasia. Microscopic sections of the defective renal tissue showed sclerosis and scattered areas of calcification.

Partial autopsy showed general infantile development. Figure 4 shows the kidneys compared with a kidney from a normal child of the same age. The former were markedly atrophic with loss of all normal markings. The sections demonstrated pronounced interstitial fibrosis with little functioning renal tissue (fig. 4). The glomeruli were included in the sclerotic process.

The second case was that of an 11 year old boy. He was also smaller than normal and throughout life showed deficient development. For a year prior to his terminal illness he had polyuria and failing vision. He had an occasional headache. During that year he had several convulsions. Studies of the blood and urine gave findings similar to those in case 2. The eyegrounds showed edema and many areas of hemorrhage. The blood pressure was about 200 systolic and 150 diastolic for two weeks before death. Roentgenograms showed diffuse osteoporosis of the long bones, with uneven rarefactions at the ends, which were later found to be islands of immature cartilage. The skull showed granular porosis associated with thickening of the cortex, causing a ground glass appearance (fig. 5). The calcium content of the blood was 8.8 mg. and the phosphorus content 5 mg. per hundred cubic centimeters about two weeks before death.

The autopsy confirmed the roentgenographic findings in the bones. There was no parathyroid adenoma. The heart was large, firm and fibrous and contained many areas of calcification. Microscopic study confirmed the gross examination

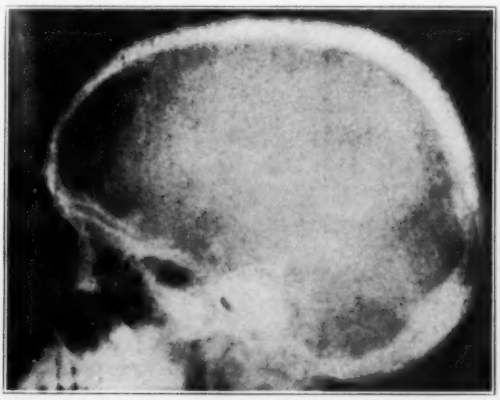

Fig. 5 (case 3).—Renal rickets. A roentgenogram of the skull, showing thickening of the cortex and the ground glass appearance of the bone.

(fig. 6). The kidneys were small, firm and granular. The cortex of the bones was thin where examined, and cross sections showed fibrous change, with scattered areas of cartilage and round cell infiltration.

Comment.—Osseous changes similar to those here reported occur in 40 to 50 per cent of these cases and when present practically establish the diagnosis.[10] The phosphorus content of the blood is high because of poor excretion of phosphorus by the damaged kidneys. Our second patient had a low calcium value, being especially low with relation to the value for phosphorus. L. G. Parsons[10] explained the situation as follows: In the usual case of renal rickets the calcium content is not

10. Parsons, L. G.: Bone Changes Occurring in Renal and Coeliac Infantilism, and Their Relationship to Rickets: I. Renal Rickets, Arch. Dis. Childhood **2**: 1 (Feb.) 1927; II. Coeliac Rickets, ibid. **2**:198 (Aug.) 1927.

extremely low, but it is always low in proportion to the phosphate content. This disproportion between the values for calcium and phosphorus acts to disturb the growth of bone. The renal function varies The excretion of phosphorus fluctuates, and deposition of bone is defective because of the change in the tides of phosphorus and calcium. There is another element that is disturbing to osseous growth, since the poor renal function makes for acidosis, which may also deter deposition of bone.[11]

There are two possible reasons why our second patient had convulsions: First, there was uremia, and, secondly, there was the low calcium content of the serum. The headaches, vomiting and ocular

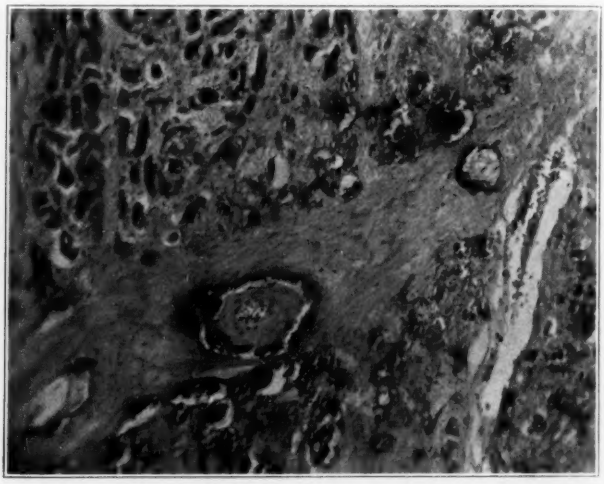

Fig. 6 (case 3).—A microscopic section of the heart, showing marked degeneration of the cardiac fibers, with numerous vacuoles. The dark-staining areas are aggregations of calcium. Note the marked fibrosis and round cell infiltration.

changes probably represented the approach toward uremia. As in our patients, marked deficiencies of height and weight are frequent in this disease.

This type of rickets results from excess phosphate and insufficient calcium in the blood plus acidosis in the presence of growing bone. Sometimes there are remissions because of improved renal function, with better excretion of phosphates. Remissions and exacerbations of the rickets usually occur because of spontaneous variations in renal func-

11. Parsons, L. G.: Rickets and Allied Diseases, Lancet **2**:485 (Sept. 8) 1928.

tion, but eventually the patient dies of uremia before the age of 20 years. Parsons [10] has warned against using ultraviolet irradiation in these cases. He has inferred that the result is increased absorption of phosphate from the bowel and disproportion between the values for phosphorus and calcium.[11] If this concept is correct, vitamin D, should, in general, be withheld in the presence of renal rickets.

CASE 4.—*Fragilitas ossium ("hereditary hypoplasia of the mesenchyme" of Key).*

A girl aged 7½ years had had fractures since the age of 18 months. She first fractured the left leg below the knee then an arm and then had various other fractures and sprains, all of which healed slowly. She had shown retarded mental and physical development. Various treatments had been tried by different attending physicians. One gave parathyroid extract for two months but the patient became weaker and was said to have become mentally unstable. Other consultants increased the calcium and vitamins in her diet.

Her mother had a pronounced deformity of the vertebral column, the diagnosis being fragilitas ossium. Both the mother and the patient's maternal half-sister had blue scleras.

When first seen the child looked sick, had a pasty complexion and a thick skin, was queer acting and had slow association of ideas. The scleras were abnormally blue. The teeth had irregular surfaces. The muscle tone was poor and as a consequence there was sagging of weight-bearing structures, resulting particularly in lumbar lordosis and exaggerated pronation of the left foot. Roentgenograms showed diffuse rarefaction of bone (fig. 7). Physical and roentgen examination showed good union at the old sites of fracture.

The basal metabolic rate was +3 per cent. The calcium content was 10 mg. and the phosphorus content 2.1 mg. per hundred cubic centimeters of blood before treatment. After treatment with liberal amounts of calcium, phosphorus and viosterol, the calcium content remained about the same, but the phosphorus content rose to 4.5 mg. per hundred cubic centimeters.

A surprising improvement was noted when she was seen three months after this treatment was started. There was great improvement in weight, health, mental activity and well-being. She had gained 10 pounds (4.5 Kg.) in the first two months of therapy. She had become energetic. School work had been difficult before, but afterward she had actually led her class in scholarship. She had had several falls without fracturing any bones. Such falls might in previous times have resulted in fractures.

The treatment was empiric and included the administration of a preparation composed of dicalcium phosphate and "bone phosphates" and also of a compound containing calcium, phosphorus and magnesium salts.[12] Egg yolk, milk and meat were emphasized in her diet. Ten drops of viosterol in oil (containing 10,000 U. S. P. units of vitamin D per gram) was given to her daily. Because of her definite improvement with this program, we believe that there may have been a real therapeutic effect, whether or not due to the rise in the phosphorus content of the blood.

12. These two preparations were, respectively, "bone salts" (Upjohn) and "phytin" (Ciba).

Comment.—General considerations in regard to this problem have been outlined by Bromer [13] and by Key.[14] The underlying cause is deficiency in the function of osteoblasts, and, as in several of the malacic diseases of bone, there is excess phosphatase in the serum.[15] Though the bones look rarefied in the roentgenograms and are soft and fragile, the quantity and proportion of calcium and phosphorus in them are

Fig. 7 (case 4).—Fragilitas ossium. This roentgenogram of the tibia and fibula is typical of the roentgenograms obtained in cases of fragilitas ossium. There is diffuse osteoporosis, which is more pronounced in the diaphysial portions. There is marked thinning of the cortical bone. The epiphyses are normal and show no pathologic change. There is a fracture in the lower portion of the tibia.

13. Bromer, R. S.: Osteogenesis Imperfecta, Am. J. Roentgenol. **20**:631 (Nov.) 1938.

14. Key, J. A.: Brittle Bones and Blue Sclera, Arch. Surg. **13**:526 (Oct.) 1926.

15. Cantarow, A.: Calcium Metabolism and Calcium Therapy, Philadelphia, Lea & Febiger, 1933. Mitchell, A. G.: Nephrosclerosis in Childhood, with Special Reference to Renal Rickets, Am. J. Dis. Child. **40**:101 (July); 345 (Aug.) 1930.

normal,[13] and the amounts of mobile calcium and phosphorus in the blood serum are also usually normal. It is as if there were ample building material for bone but a poor arrangement of that material by the osteoblasts, with fragile structures resulting. Endocrine influences are speculative only. Some children with this disease improve spontaneously during adolescence.[16] The finding of a low phosphorus content of the serum of our patient and the improvement with forcing of phosphorus may be worth considering in other similar cases.

CASE 5.—*Parathyroid adenoma.*

A 45 year old woman was seen in a short terminal illness only. Although the clinical data are incomplete, the cause of her death and the autopsy data warrant this account. She entered the hospital in December 1934, suffering from a fractured femur which had resulted from a fall. The fracture and the roentgenographic appearance of the bone are shown in figure 8 *A*. While in bed, with the injured leg in an extension appliance, she was shifting her weight with the aid of a hand trapeze when suddenly the left side of the thoracic cage collapsed. There were nine fractures on that side, as shown roentgenographically. She died several days later as a result of pulmonary collapse and the pneumonia which followed. The only medical information obtained from prior consultants was that her basal metabolic rate had been normal and she had had some type of anemia when examined a year previously.

Roentgenograms showed diffuse demineralization of all the bones studied, including the skull, thorax, arms, pelvis, hips, foot and one ankle (fig. 8). There were numerous fractures, including those of the hip and ribs, which occurred just before death.

Postmortem examination showed a thin woman with delicate features, thick glossy hair and tapering fingers. Some of the recent fractures were observed directly, and there was no evidence of healing. She had no obvious exophthalmos.

The thyroid and parathyroid glands are shown in figure 9. The thyroid gland weighed 80 Gm. It was firm, meaty and hyperplastic, both grossly and microscopically. The acinar epithelium showed definite infolding and feathering, as observed in the microscopic sections. There were also moderate fibrosis and some round cell infiltration. There was a thyroid adenoma, which measured 2 by 3 cm. In the right posterior region was a parathyroid adenoma, the shape of an egg, which measured 2 by 3 cm. It was somewhat fluctuant and cystic and contained a sanguineous fluid. The adenoma was yellowish, and its wall varied from 2 to 5 mm. in thickness. There was only one other parathyroid gland, the left inferior one; it showed a normal size and shape. The microscopic sections of the parathyroid adenoma showed some fibrosis, interstitial hemorrhage and a typical parathyroid structure, with definite hyperplasia (fig. 9 *B*). The bones generally were soft and cut easily. The ribs could be sectioned with ordinary shears. They showed complete replacement by fibrocartilaginous tissue. The right adrenal gland was moderately hyperplastic, and the left one was markedly so. It was approximately four times larger than normal. Microscopic study of the larger adrenal gland showed the hyperplasia noted grossly but no other significant abnormality. The hyperplasia was most marked in the cortex.

16. Hills, R. G., and McLanahan, S.: Brittle Bones and Blue Scleras in Two Generations, Arch. Int. Med. **59**:41 (Jan.) 1937.

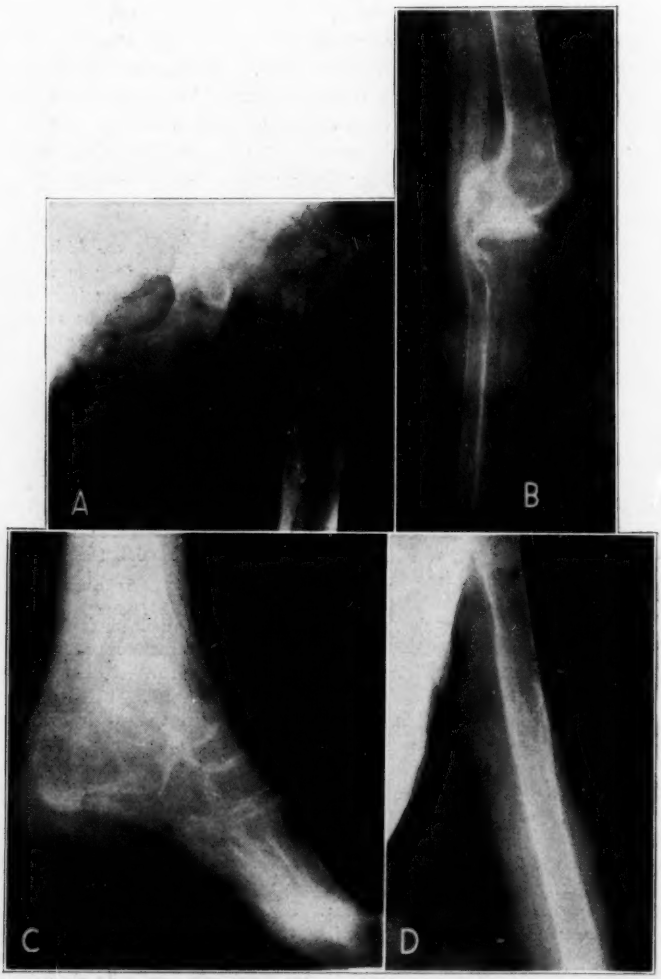

Fig. 8 (case 5).—Parathyroid adenoma, with hyperplasia of the thyroid and adrenal glands. *A*, a roentgenogram of a portion of the pelvis and femur, displaying diffuse demineralization and fracture of the neck of the femur. Note the absence of cyst formation, which is usually seen in cases of uncomplicated hyperparathyroidism. *B*, a view of the knee, showing demineralization. There is no fracture. *C*, a view of the foot and ankle, showing demineralization. *D*, diffuse demineralization of the humerus, with fracture of the upper third, which occurred spontaneously.

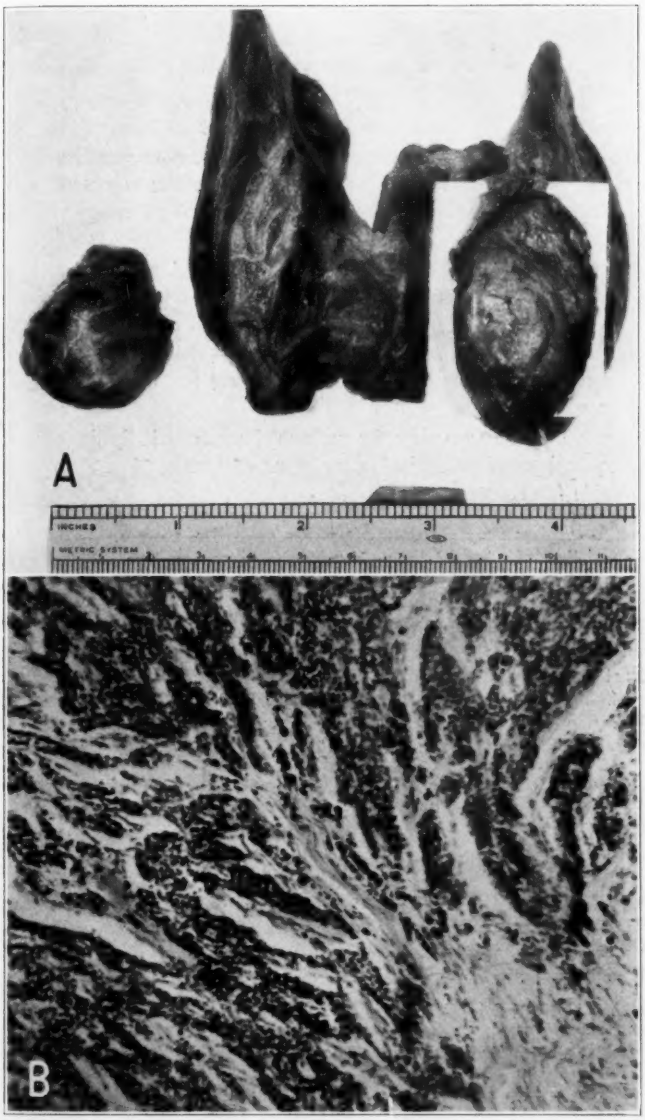

Fig. 9 (case 5).—*A*, a posterior view of the thyroid gland, showing the parathyroid adenoma set off by an oblong white background (autopsy specimen). Note the diffuse enlargement of the thyroid gland due to hyperplasia. The parathyroid adenoma is yellow, discrete and encapsulated, having undergone central cystic degeneration. The separate mass to the left is an adenoma of the thyroid gland. *B*, a microscopic section of the parathyroid adenoma, showing diffuse hyperplasia, with moderate interstitial fibrosis. There are a relative decrease in the cells of the acidophilic type and a relative increase in the basophilic cells.

The diagnoses included the following: parathyroid adenoma, thyroid hyperplasia, thyroid adenoma and hyperplasia of the adrenal glands.

Comment.—Most patients with hyperparathyroidism show cystic changes in the bone. This patient showed diffuse demineralization, and this change may conceivably have resulted from the combined effects of the parathyroid adenoma and thyrotoxicosis.[17] The decalcification of thyrotoxicosis is diffuse.

The pituitary gland should have been inspected at autopsy. Basophilic adenoma of the pituitary gland is associated with osteoporosis. It is also associated with hypertrophy of the adrenal cortex.[17] Was there pituitary basophilism in addition to the hyperthyroidism and the parathyroid adenoma to account for the astounding softening of the bones in this case?

There is no need to review the various characteristic findings in cases of hyperparathyroidism. The observations of Shelling [18] and of Barr [19] are valuable for reference.

CASE 6.—*Diffuse bony metastases from a renal cell carcinoma.*

In the fall of 1935 a 60 year old physician was seen because of a variety of complaints. He had pain in the lower portion of the back, lassitude, mental confusion, anorexia and palpitation. Roentgenograms showed diffuse rarefaction of the bones in the lower portion of the back and moderate decalcification of the sternum and ribs. There was nothing clinically to suggest thyrotoxicosis, an occasional cause of diffuse demineralization of bones. Parathyroid overactivity was suspected. The calcium content of the serum was 16 mg and the phosphorus content 3.2 mg. per hundred cubic centimeters. Study of the calcium balance proved that there was an actual calcium deficit. There was a negative balance of 3,474.8 mg. in five days of study.

Date	Intake, Mg.	Output in Urine, Mg.	Output in Feces, Mg.
Oct. 20	302	10.0	717
21	135	38.3	1,015
22	245	38.3	1,015
23	496	25.1	1,047
24	325	25.1	1,047
Totals	1,503	136.8	4,841

These findings strengthened the suspicion of parathyroid overactivity. There was no abnormal mass in the parathyroid region. The possibility of aberrant parathyroid tissue in a normal position or in the mediastinum was strong enough

17. Zondek, H.: Diseases of the Endocrine Glands, Baltimore, William Wood & Company, 1935. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: Studies of Calcium and Phosphorus Metabolism: Effects of Thyroid Hormone and Thyroid Disease, J. Clin. Investigation **7**:97 (April) 1929.

18. Shelling, D. H.: The Parathyroids in Health and Disease, St. Louis, C. V. Mosby Company, 1935.

19. Barr, D. P., and Bulger, H.: The Clinical Syndrome of Hyperparathyroidism, Am. J. M. Sc. **179**:449 (April) 1930.

to warrant exploration. The patient was referred to Drs. Henry Christian, Joseph Aub and Edward D. Churchill, at the Peter Bent Brigham Hospital, Boston.

Twelve years before this illness he had had surgical removal of the left kidney for renal cell carcinoma. No symptom or sign suggested any recurrence of this except that the possibility of metastasis to the bone was casually considered. It was thought unlikely that there would be recurrence or metastasis after twelve years of health following this first surgical treatment.

When Dr. Churchill explored for abnormal parathyroid tissue, nothing of pathologic significance was found. The patient died eleven days after operation. At autopsy a recurrence of renal cell carcinoma was seen at the operative site, and metastasis of the neoplasm to rarefied bones was proved.

Comment.—In this case the pain in the lower portion of the back was attributed to metastatic neoplasm seen at autopsy, with no necessary correlation with the perverted calcium metabolism. The lassitude and mental confusion probably depended on more than one cause. The patient was toxic and sometimes had moderate fever. He was a nervous person, and the toxemia may have caused the mental changes, in whole or in part. But the abnormally high calcium content of the blood may also have contributed to these effects, as is suggested by the behavior of a boy who had an overdose of parathyroid extract.[20] His "palpitation" was variable. One electrocardiogram showed a rate near 30 per minute, with normal complexes; another showed absolute arrhythmia at a rate near 100 per minute, with auricular fibrillation. An abnormally high calcium content of the serum may have caused each of these cardiac variations. A high calcium level has been reported to depress the sino-auricular node, but it also predisposes to ectopic beats.[21] The anorexia may have been due to toxemia or a high calcium content [20] or both.

Although in this patient calcium was probably assimilated normally and deposited satisfactorily in the bones, some of the bones were giving up calcium to the blood stream too rapidly because of the malignant bony metastases. The roentgenograms showed diffuse rarefaction of the bones (fig. 10).

In cases of parathyroid disease the rarefaction is usually cystic, and the loss of calcium is in the urine rather than in the stool.[22] Our patient's rarefaction was not cystic, and he lost relatively little calcium in the urine. Was the rarefaction due to an overactive thyroid gland? This is unlikely, because he did not have hyperthyroidism clinically and, again, the loss would have been principally by way of the urine.[23] Was

20. Lowenburg, H., and Ginsburg, T. M.: Acute Hypercalcemia, J. A. M. A. **99**:1166 (Oct. 1) 1932.

21. Sampson, J. J., and Anderson, E. M.: The Treatment of Certain Cardiac Arrhythmias with Potassium Salts, J. A. M. A. **99**:2257 (Dec. 31) 1932.

22. Aub, J. C.: The Importance of Calcium Metabolism in Internal Medicine, Proc. California Acad. Med. **1**:74, 1930.

23. Aub, J. C.: Calcium and Phosphorus Metabolism, in Harvey Lectures (1928-1929), Baltimore, Williams & Wilkins Company, 1930, p. 151.

it due to disuse? Probably not, because with complete confinement in bed one would expect a more uniform rarefaction than the roentgenograms showed. These queries are valuable with respect to the corrected point of view made possible by the autopsy data on malignant involvement of bone.

This report is included because of the antemortem quandary and the postmortem answer and because of the interesting effect that a high calcium content of the serum may have on the function of soft tissue.

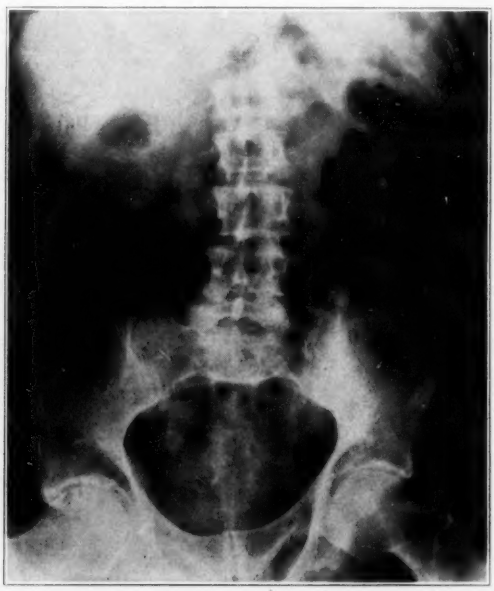

Fig. 10 (case 6).—Metastatic carcinoma from primary renal cell carcinoma. Marked generalized osteoporosis is present. The osteoporosis is not typical of hyperparathyroidism and is more marked than that usually noted in a normal patient of this age. A generalized osseous metastatic carcinoma was present at postmortem examination.

CASE 7.—*Senile osteomalacia.*

In July 1931 a 65 year old woman, who worked as a maid in a hospital, fell to a sitting position and immediately had pain in the upper lumbar region of the spine. She was found to have a compression fracture of the first lumbar vertebra. All vertebrae visible in the roentgenograms showed decalcification. After months of orthopedic care she was gradually moved from bed; but with weight bearing, several other vertebrae became compressed, and her back was intolerably painful. More orthopedic measures followed, and medical investigation revealed the fact that in ten days she lost 7 Gm. more calcium than she received in her food. This loss was probably not due to a digestive fault, because the stools contained almost

no fat and she had no diarrhea. Calcium and phosphorus were present in normal amounts in the blood. It was therefore assumed that there was some difficulty in fixing or retaining calcium in the bones, and treatment was directed with that possibility in mind. In order to be sure of an adequate supply of these elements she was given increased amounts of calcium and phosphorus in the food, in the form of milk and eggs. She was given lactose in order to favor absorption.[24] She was also given 0.5 cc. of viosterol in oil three times daily (a total of 60,000 U. S. P. units per day) for six months. In order to decrease lysis of bone by parathyroid hormone, the parathyroid region was irradiated four times at intervals of one week, with 430 roentgens given at 200 kilovolts with a 0.75 mm. copper filter (about 200 roentgens on each side). Another study of the calcium balance was carried out during this period of therapy, as outlined, about two months after the last roentgen treatment, and it was found that she then retained calcium. In twelve days she excreted 0.5 Gm. less calcium that she took in her food. After this she was again gradually moved from bed, this time with success. She was seen one year after this period of orthopedic care and confinement in bed and reported that

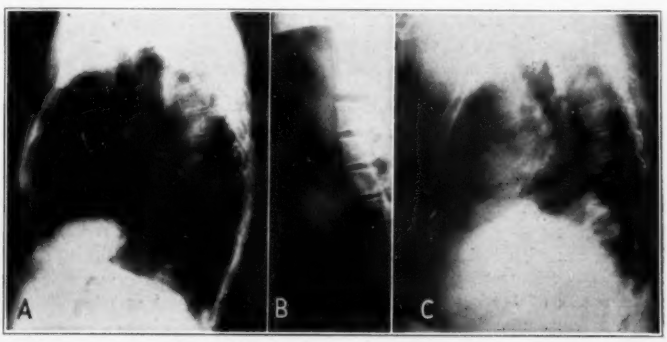

Fig. 11.—Senile osteomalacia. *A*, a lateral view of the patient's spine prior to treatment. *B*, a lateral view of the spine of a person of the same sex and age as the patient (an attempt was made to use an identical technic). *C*, a lateral view of the patient's spine after two years of treatment.

she was doing light housework without interruption. She required no orthopedic support of any sort. Roentgenograms of the vertebrae showed slightly more density than previously (fig. 11).

Collateral findings were not of significance except that she had moderate hypertension and moderate sclerosis of the retinal vessels. There was nothing to suggest hyperthyroidism. The basal metabolic rate was +3 per cent. There was no palpable parathyroid tumor and, as mentioned before, the calcium and phosphorus levels of the blood were normal.

Comment.—Patients with this type of disorder are numerous and usually do not improve with treatment. Clinical improvement in this case was undoubted. The roentgenograms and the quantitative study

24. Bergeim, O.: Intestinal Chemistry: Carbohydrates and Calcium and Phosphorus Absorption, J. Biol. Chem. **70**:35 (Sept.) 1926.

of the calcium are subject to error and fallacy, despite attempts to make the comparisons quantitatively accurate. The amounts of viosterol given were suggested by success in the treatment of intractable rickets with large doses [25] and by some of the experimental work of Shelling, in which small doses of vitamin D caused poor calcification of bone; larger doses, hypercalcification, and still larger doses, decalcification.[26] We might now hesitate to give these amounts.[27] A physician of this community died, with polyuria, weakness and anorexia, after taking 2,500,000 U. S. P. units daily for seventeen days.[28]

CASE 8.—*Tetany in an adult.*

In April 1929, during rounds of the wards at the Alameda County Hospital, an intern called attention to a patient whose principal complaint was of diarrhea. She was a nervous, inadequate person, weighing only 83 pounds (37.6 Kg.) and being 5 feet and 4 inches (162.5 cm.) tall. The principal pathologic findings were hypochromic anemia, achlorhydria, poor nourishment, poor posture and nervousness. She was discharged from the hospital. Five months later she called for help at her home because of muscular cramps.

She presented a dramatic physical picture of tetany. Her mouth was dry, and the muscles were so stiff that she could scarcely talk. The upper eyelids were retracted. The arms were rigidly straight, the hands dorsally flexed on the forearms and the fingers tightly clenched. All accessible muscles were involuntarily tense. The legs were stiff and straight, and the feet were in ventral flexion, so that they almost continued the straight line of the leg. The Chvostek and Trousseau signs were not at first obtainable, presumably because of extreme rigidity, but later they were elicited, when treatment had resulted in some relaxation. This condition had come on gradually for several days. She was greatly and justifiably frightened. Her muscles pained, and she was thoroughly aware of the progression of her condition. Two cubic centimeters of parathyroid extract was injected intramuscularly, and she was sent back to the hospital. After arrival there she was given calcium chloride intravenously and rapidly lost the discomfort due to the tetany. The calcium content of the blood was 5.3 mg. per hundred cubic centimeters.

She was given a diet low in roughage. Sedatives and camphorated tincture of opium were administered in order to control the diarrhea. She was given food which provided large amounts of calcium, together with 15 grains (0.97 Gm.) of calcium lactate three times per day. Thirty drops of diluted hydrochloric acid and 5 drops of viosterol were taken with each meal. Ten cubic centimeters of 5 per cent solution of calcium chloride was injected intravenously three times during the first three days. She began improving symptomatically with the first

25. Jampolis, M., and Londe, S.: Need of Larger Doses of Viosterol in Severe Rickets (Osteomalacia Type): Comparative Study of Efficiency of Viosterol and Cod Liver Oil, J. A. M. A. **98**:1637 (May 7) 1932.

26. Shelling, D. H., and Asher, D. E.: Calcium and Phosphorus Studies: Relation of Calcium and Phosphorus of Diet to Toxicity of Viosterol, Bull. Johns Hopkins Hosp. **50**:318 (May) 1932.

27. Reed, C. I.: Symptoms of Viosterol Overdosage in Human Subjects, J. A. M. A. **102**:1745 (May 26) 1934. Leake, C. D.: Vitamin D Toxicity, California & West. Med. **44**:149 (March) 1936.

28. Kerr, W. W.: Personal communication to the authors.

dose. After eight days the calcium content of the serum was 8 mg. per hundred cubic centimeters, and eleven days later it was 10 mg. per hundred cubic centimeters. Exposures to a quartz mercury vapor lamp were used. During a stay of two months in the hospital she gained consistently in weight and well-being. She has had no recurrence of tetany in the six and one half years since her discharge.

At present her general condition is better. She now weighs consistently about 105 pounds (47.6 Kg.). Diarrhea returns at times but is usually controlled by the use of 25 drops of diluted hydrochloric acid with meals plus ½ grain (0.03 Gm.) of phenobarbital once or twice daily. She had been able to work and to support herself during most of the time since her discharge from the hospital. Nervousness and diarrhea constitute a menacing sequence at times. The calcium content of the serum one year after her acute attack was 10.4 mg. per hundred cubic centimeters. She has taken calcium lactate or calcium gluconate (30 grains [1.94 Gm.] per day) and viosterol (10 drops per day) at various times since her acute illness.

A roentgenogram of the gastrointestinal tract showed nothing of interest except that the colon was redundant. The stool showed one or two fat droplets per high power (dry) field and no protozoa. A roentgenogram of the hand showed normal density of the bones. A determination of the phosphorus content of the blood was made. The value was 2 mg. at a time when the calcium content was 8 mg. per hundred cubic centimeters. The basal metabolic rate was —17 per cent. An alcohol test meal showed no free hydrochloric acid. A blood count showed hypochromic anemia.

Comment.—It is our impression that this patient had a fault in the absorption of calcium through the intestinal wall and that diarrhea was a possible factor therein. Lack of gastric hydrochloric acid may have contributed by favoring the diarrhea and by decreasing the solubility of the calcium in the lumen of the intestine. This patient suffers from nervous hypertension, and an imbalance of the vegetative nervous system may have contributed to the diarrhea. Reassurance and sedation probably helped in this respect.

The gastric anacidity and diarrhea may also have contributed to the anemia, and the anemia may have been on a nutritional basis even with an adequate menu. The net result of an inadequate diet or an adequate diet poorly absorbed may be the same. A normal intake of food, the use of reduced iron and also the better availability of calcium probably united to help the anemia.[29]

The injection of parathyroid extract at the height of the tetany was not ideal treatment, since this drug has a four hour period of latency. Calcium chloride should have been given intravenously and was used soon afterward. Viosterol was given to furnish vitamin D, which is said to improve absorption of calcium.[11] Lactose was used to help the absorption of calcium also.[24]

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29. Orten, J. M.; Smith, A. H., and Mendel, L. B.: Relation of Calcium and of Iron to Erythrocyte and Hemoglobin Content of Blood of Rats Consuming Mineral Deficient Ration, J. Nutrition **12**:373 (Oct.) 1936.

We assume that this patient had poor absorption of food and metabolites and that this was due to (*a*) the abnormally rapid motility of the digestive content and (*b*) the lack of gastric hydrochloric acid. Of interest is the fact that she was one of twins. She had rickets as a child, and her sister, with an identical menu, did not. Also there was a history of soreness of the tongue, peeling of the fingers and melancholia along with diarrhea in 1927. The diagnostic impressions were tetany, achlorhydria, hypochromic anemia, undernourishment, class D posture, preexisting rickets and pellagra, suspected from the history.

CASE 9.—*Paget's disease (osteitis deformans).*

The patient was a 52 year old man. Two years before entry he first noticed pain and discomfort in the right knee and leg on walking. One and one-half years before entry the legs were noticeably bowed, and he had a moderate limp. Some of his bones felt sore when he was lying in bed, and the bones of the legs hurt when he walked.

His health had been good until the present symptoms began. Since that time he had gradually become more and more incapacitated. There was a history of malaria and typhoid many years before entry. He was 5 feet and 10 inches (177.8 cm.) tall and weighed 155 pounds (70.3 Kg.). Systematic general examination revealed nothing abnormal except bony changes. Roentgenograms showed rarefaction, deformity and density (figs. 12 and 13). The measurements of the right and left legs were equal.

No significant abnormality of the vascular system was found. The laboratory reports on the blood were as follows:

	Protein, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Phosphatase, Bodansky Units per 100 Cc.	
March 11, 1937..	2.2	11.3	43.5	(normal upper limit near 7 units)
April 30, 1937..	3.9	10.7		
Aug. 30, 1937..	3.3		65.0	

Renal calculi were not suggested by the history, examination of the urine or roentgenograms.

Deep application of heat by radiothermy lessened his pain. He improved symptomatically with a diet high in calcium. Neither of these measures can be considered specific.

Comment.—This case report is included because there was a malacic disease of the bone. There was a lowered calcium content in the involved bone.[30] An abortive form of osteitis fibrosa cystica may be confused with Paget's disease. Active osteitis fibrosa cystica is usually associated with an abnormally high calcium content and low phosphorus content of the serum. In both cases there is an abnormally high phosphatase content of the plasma, Paget's disease being accompanied by a higher average content than osteitis fibrosa cystica. A high phosphatase content of the

30. Kay, H. D.; Levy-Simpson, S.; Riddoch, G., and Vilvandré, G. E.: Osteitis Deformans, with Roentgenologic Section, Arch. Int. Med. **53**:208 (Feb.) 1934.

plasma is characteristic of several malacic diseases of bone. It is probably a result rather than a cause of Paget's disease.[31] The probable principal function of phosphatase is to liberate inorganic phosphate from phosphoric esters, making inorganic phosphorus available for bone formation. In the malacic diseases of bone the phosphatase is truant. There is a

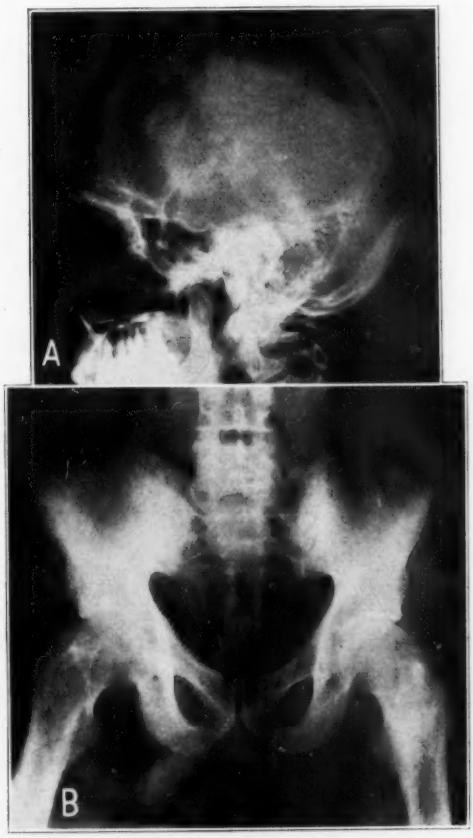


Fig. 12 (case 9).—Paget's disease. *A*, a roentgenogram of the skull. Note the large, irregular rarefaction in the left frontal bone, in the pattern described as that of osteomalacia circumscripta. *B*, a roentgenogram of the plevis and femurs. Note the diffuse rarefaction of the right ilium, the various zones of rarefaction elsewhere and the increased width of the right ilium.

31. Cantarow, A.: Review of Phosphatase Activity and Calcium and Electrolyte Metabolism, Internat. Clin. **1**:230 (March) 1936.

low content of it in the bone, with an increased amount in the plasma.[32] There is no successful treatment for Paget's disease. Many practical details were noted by Gutman [32] in a review of 116 cases. Irradiation may ease local pain, but remissions of symptoms are common and improvement after treatment may not be due to the treatment.

Fig. 13 (case 9).—Paget's disease. Roentgenograms showing bowing of the softened, weight-bearing femur, with secondary thickening of the cortex due to osteitis.

COMMENT

From these widely separated clinical experiences, the calcium metabolism of the organism is viewed from a variety of positions. Some of the complex relations of the minerals in human metabolism are studied at the bedside.

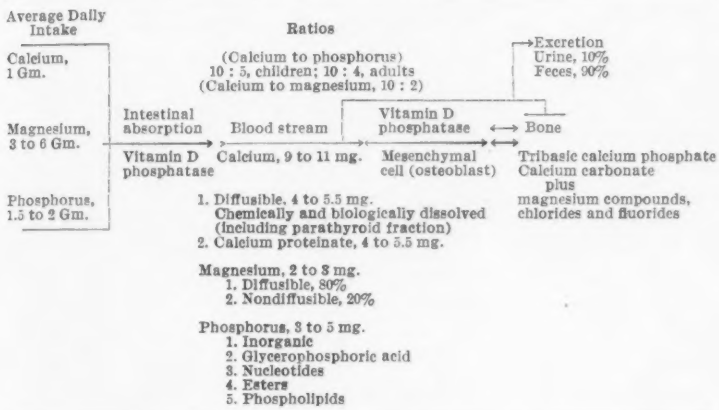
One should suspect disturbance of mineral metabolism when there is defective nutrition. A child of subnormal stature may have congenital renal insufficiency, with a fault in the excretion of phosphate, as in renal rickets. A thin woman with diarrhea may be losing calcium, to the disadvantage of the function of the soft tissues; tetany may develop. A poorly nourished person with anemia may have poor absorption of iron or of calcium from the digestive tract. The food eaten may contain too little of these elements.

32. Gutman, A. B., and Kasabach, H.: Paget's Disease (Osteitis Deformans): Analysis of One Hundred and Sixteen Cases, Am. J. M. Sc. **191**:361 (March) 1936.

Unusual fractures may be due not only to primary or secondary neoplasm in bones but to poor internal economy of calcium or of phosphate. A parathyroid adenoma or parathyroid hyperplasia may be the cause. Poor functioning of the osteoblasts may be the reason for the presence of rarefied bones which fracture too easily, as in case 4 (fragilitas osseum). There may be a lack of ability to deposit available calcium in bone, as we presume to be the case in senile osteomalacia.

A tonic convulsive state may be due to a lowered calcium content of the serum, as in our extremely tetanic patient. Convulsions may result from both uremia and low calcium values, as was possible in the case of our patients with renal rickets.

Metabolic Sequences of Alkali Earth Metals



A high calcium content may cause or predispose to an abnormally slow cardiac rate or to rapid, irregular cardiac action. Both effects were postulated in our patient with a high calcium content secondary to metastatic carcinoma of bone. If long sustained, the high calcium value may cause precipitation of calcium salts in soft tissue, as in the cardiac muscle in case 5 (parathyroid adenoma). The occurrence of renal and ureteral stone under like circumstances is a matter of considerable current comment.

Not all spurious deposits of calcium salt are traceable to overabundance of calcium in the blood. In calcinosis and several allied diseases the calcium and phosphate contents of the serum are normal. For some reason there are points of diminished tissue viability in these patients. Defective local circulation may be the reason. These regions become progressively buried in calcium salt.

In cases in which bone is abnormally rarefied phosphatase is often present in the serum to excess. Phosphatase frees inorganic from organic phosphate for use in bone building. One would suppose, then, that when bone is deficient in calcium phosphate the body must be trying to provide excess phosphatase and thus encourage the deposit of calcium phosphate. But the increased supply does not always reach its goal in large quantity. In Paget's disease, phosphatase is present in the bone in less than normal amount.

When there is a suspicion of deranged mineral metabolism, the important facts can usually be obtained at the bedside with the aid of the laboratory and roentgenographic facilities in a class A hospital.

Some of the facts of human mineral metabolism are recorded in the accompanying table.

RENAL AMYLOIDOSIS

A FURTHER STUDY OF THE CLINICAL COURSE AND PATHOLOGIC LESIONS IN FIFTY-SEVEN CASES

HUGO O. ALTNOW, M.D.
MINNEAPOLIS
AND
CHARLOTTE C. VAN WINKLE, M.D.
AND
SUMNER S. COHEN, M.D.
OAK TERRACE, MINN.

In 1935 we [1] reported on 16 patients with renal amyloidosis for whom a clinical diagnosis had been made during life and had been verified by postmortem examination. These patients had been observed by us over a period of two to eight years, their records were reviewed and the data were tabulated with regard to the type of tuberculosis in which renal amyloidosis occurs, the likely precipitating factors, the urinary findings and renal function, the blood pressure, the physical findings and the condition of the eyegrounds, together with pertinent necropsy data and information regarding the distribution of amyloid in the kidney. In this way we attempted to portray the clinical life history in cases of renal amyloidosis as it occurs among patients with tuberculosis.

In this paper we are reporting on 41 additional patients with renal amyloidosis. Five of these belong to the aforementioned group, making a total of 21 patients for whom the clinical diagnosis of renal amyloidosis was confirmed at postmortem examination. The remaining 36 were those for whom a clinical diagnosis was not made during life, for the following reasons: (1) oversight and inadequate follow-up study, (2) a confusing clinical picture and findings, (3) our inexperience and an insufficiently high threshold of suspicion in the beginning of our study and (4) findings not sufficient for a clinical diagnosis of renal amyloidosis. This series comprises a total of 57 patients with pathologically proved amyloidosis. It is our purpose to analyze these cases in order to add to the clinical picture, to call attention to certain features about the disease that were probably overemphasized by us and to comment on the reasons for our failure to make a proper clinical diagnosis when this

From the Nicollet Clinic, Minneapolis, and the Glen Lake Sanatorium, Oak Terrace, Minn.

1. Altnow, H. O.; Van Winkle, C. C.; Maly, H. W., and Williams, L. E.: Renal Amyloidosis, Arch. Int. Med. **56**:944 (Nov.) 1935.

occurred and was avoidable. We are also presenting herewith a diagnostic schema which, we believe, will be of considerable aid in the earlier recognition of the less advanced stages. Since this paper supplements the data of our first publication, the same form of presentation will be used.

In the accompanying tables the 21 patients for whom the diagnosis was made and confirmed at postmortem examination are segregated as group 1 and the 36 patients for whom we failed to make the diagnosis, for one reason or another, as group 2.

In table 1 the data for the 57 patients show the nature of the cases of tuberculosis in which renal amyloidosis is found. Forty-seven patients had far advanced pulmonary tuberculosis, 4 had moderately advanced pulmonary tuberculosis and 6 had Pott's disease without pulmonary tuberculosis. One patient with far advanced and 1 with moderately advanced pulmonary tuberculosis had Pott's disease, and 1 with far advanced pulmonary tuberculosis had tuberculosis of the bones of the legs, making a total of 9 patients with tuberculosis of the bones (15.7 per cent).

Suppurating foci were present in the following cases: empyema, 7; Pott's disease, 8; tuberculosis of long bones, 1; draining sinuses from tuberculous kidney, 1, and tuberculous peritonitis with draining sinuses, 1. Eighteen patients, or only 31.5 per cent, showed suppurating foci. If cavitation of the lung is so considered, then each of the patients had a suppurating focus.

The outstanding complication was tuberculous enteritis. A clinical diagnosis based on symptoms and suggestive roentgen findings was made in 33 instances, but 13 of these diagnoses were not verified by postmortem examination. However, in 5 of these cases, amyloid infiltration of the intestinal wall was present. We believe that amyloid infiltration may produce gastrointestinal symptoms that simulate tuberculous enteritis. If only pathologically verified cases are considered, the incidence of tuberculous enteritis was approximately 60 per cent; and if amyloid infiltration of the intestine is added (which includes all cases in which there was a pathologic basis for the symptoms), the incidence was 70 per cent. A clinical diagnosis based on gastrointestinal symptoms, namely, an unexplained inability to gain weight, anorexia, nausea, flatulence, alternating constipation and diarrhea, and intermittent or persistent diarrhea, associated with cramping pain in cases of more advanced involvement, and suggestive roentgen findings was made in 57.5 per cent of the cases. Enteritis was present in 82 per cent, if unverified clinical cases (8), amyloid infiltration of the intestine (5) and pathologically proved cases (34) are included.

Tuberculosis of the appendix occurred in 16 of 51 patients, or in 31 per cent (6 had prior appendectomy). It was present 4 times inde-

pendently of tuberculosis of the intestines, and in 3 of these instances a diagnosis of enteritis had been made. Tuberculosis of the appendix may have been responsible for the production of the symptoms that led to the clinical diagnosis of enteritis.

The clinical diagnosis of rectal tuberculosis was made 9 times, confirmed in 3 cases and discovered at necropsy in 2 instances.

A clinical diagnosis of tuberculous laryngitis was made in 15 cases and discovered post mortem in another case. The rectum and larynx were not routinely examined post mortem.

Enlargement of the lymph glands sufficient for the clinical diagnosis of adenitis occurred 6 times, but enlarged lymph glands in regions inaccessible clinically were observed at necropsy 45 times, or in 79 per cent of the cases.

Pleural effusion was recognized by clinical methods 12 times and tuberculous pleuritis once. In 3 of these cases the effusion disappeared before death. Seven of these patients were considered as having empyema, and 1 was considered as having healed empyema. Thirteen additional patients showed effusion post mortem which had not been recognized by clinical methods. Active pleural involvement was therefore present in 26 patients (46 per cent). Tuberculous pericarditis was found at necropsy in 9 instances. A clinical diagnosis of tuberculous peritonitis was made in 1 case, but in 14 additional cases it was discovered at postmortem examination. Thirty-six patients, or 65 per cent, showed pleuritis, pericarditis or peritonitis alone or in combination, with the diagnosis established by either clinical or postmortem examination or both. This figure serves to emphasize the fact that tuberculosis of the serous membranes is an important complication.

Tuberculous infection of the kidney was present in 12 patients, and 10 showed other renal lesions (table 1).

PROBABLE PRECIPITATING COMPLICATIONS

There were 46 patients for whom the date of the presumptive or definite onset (or both) could be determined with reasonable accuracy (table 2). An outstanding clinical event or complication that might be associated with the onset of renal amyloidosis occurred 25 times (54 per cent), contrasted with an incidence of 87 per cent in the 16 cases formerly reported. This can probably be accounted for by the fact that in the patients in this group the onset was generally more insidious and the clinical picture less fully developed. The onset of clinical enteritis as a probable precipitating factor also became less conspicuous.

ALBUMINURIA

Ten patients showed no albuminuria, but for 2 the period of observation was short. In 47 patients with albuminuria the average duration

TABLE 1.—*Primary Lesions and Suppurating Foci, with Complication Noted Clinically and at Autopsy, Exclusive of Amyloidosis* *

Group	Case	Primary Diagnosis	Suppurating Focus	Tuberculous Lesions: Gastrointestinal Tract: Enteritis	Appendix	Rectum	Larynx	Adenitis	Serous Membrane: Pleural Effusion	Pericarditis	Tuberculous Peritonitis	Renal Complications	Other Lesions
1	1	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	c	c	a	..	..	..		
	2	Pott's disease (ca)	Psoas (ca)	..	..	..	..	ca	c	..	..		
	3	Pott's disease (ca)	Psoas (ca)	..	..	..	..	a	..	..	..		
	4	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	..	a	a	a	..	..		
	5	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	ca	..	a	..	..	..	Nontuberculous abscess (a)	
	6	Far advanced pulmonary tuberculosis with cavitation (ca)	Empyema (ca)	a	a	..	..	a	ca	..	..	Tuberculous kidney (ca)	Miliary tuberculosis (a); syphilis (c); tubercle of heart (a)
	7	Far advanced pulmonary tuberculosis (ca)	Sinuses (ca)	a	a	..	..	a	..	a	..	Tuberculous kidney (ca)	Retroperitoneal abscess (a)
	8	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	a	..	c	..	..	..	a		
	9	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	..	a	c	a	..	a	..	.....	Tuberculous bronchiectasis (c); otitis media (c)
	10	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	a	ca	..	..	..	a	..	Mild chronic nephritis (ca)	
	11	Far advanced pulmonary tuberculosis with cavitation (ca)	Empyema (ca)	ca	..	..	..	ca	ca	..	a	Mild chronic nephritis (ca)	
	12	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	..	c	..	a	a	..	Chronic nephritis (ca)	Syphilis (c)
	13	Moderately advanced pulmonary tuberculosis (c)	.....	..	..	..	c	..	..	..	..	Chronic nephritis (ca)	Carcinoma of lungs (a); metastasis to bone (a)
	14	Moderately advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	c	..	a	c	a	..	Chronic nephritis (ca)	Pancreatitis (a)
	15	Pott's disease (ca)	Psoas (ca)	c	..	..	..	a	..	..	..	Chronic nephritis (ca)	Pancreatitis (a)
	16	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	..	a	..	..	a	..	..	..	Chronic nephritis (ca)	Encephalomalacia (ca); infarct of spleen (a); mural thrombosis of heart (a)
	17	Far advanced pulmonary tuberculosis with cavitation (ca)	Empyema (ca)	c	..	..	..	a	ca	..	..	.....	Pleural pocket filled with fluid (a)
	18	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	..	c	..	a	..	..	..		
	19	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	a	..	..	a	a	..	a	.....	Tubercles of tubes (a)
	20	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	a	..	..	a	c	..	..	.....	Syphilis (c)
	21	Far advanced pulmonary tuberculosis with cavitation (ca)	Empyema (ca)	c	x	..	..	..	ca	..	..	.....	Tuberculous meningitis (ca)
2	22	Far advanced pulmonary tuberculosis with cavitation (ca)	Left leg and right knee (ca)	ca	..	..	..	a	..	..	a	Tuberculous kidney (ca)	Thoracoplasty; tuberculous epididymitis (ca)
	23	Pott's disease (ca)	Psoas (ca)	..	..	..	..	..	..	..	..	.....	Paravertebral sinus (a)
	24	Pott's disease (ca)	Psoas (ca)	..	..	..	..	a	..	..	..		
	25	Far advanced pulmonary tuberculosis with cavitation (ca)	Empyema (ca)	ca	a	..	c	a	ca	..	a	.....	Cervical adenitis (c)
	26	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	..	..	..	a	..	..	..		
	27	Far advanced pulmonary tuberculosis (ca)	.....	..	..	..	..	..	..	..	..	Tubercles and carcinoma	
	28	Far advanced pulmonary tuberculosis (ca)	.....	c	..	..	c	a	..	..	a	Tubercles (a)	

27	Far advanced pulmonary tuberculosis (ca)	.....	..	..	..	..	..	..	..	..	Tubercles and carcinoma	
28	Far advanced pulmonary tuberculosis (ca)	.....	c	..	..	c	a	..	..	a	Tubercles (a)	
29	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	a	..	c	a	a	..	..		
30	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	x	c	c	c	..	..	..	Tubercles and infarct (a)	Tuberculoma of spinal cord and pancreatitis (a)
31	Far advanced pulmonary tuberculosis with cavitation (ca)	Tuberculous peritonitis (ca)	ca	..	c	..	a	ca	..	ca	Tuberculous kidney (ca)	
32	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	..	..	c	a	a	a	..		
33	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	..	..	..	..	..	..	a	Tubercles and thrombosis (a)	Tuberculous toe joint (ca)
34	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	c	a	..	ca	a	ca	..	..	Thrombosis (a)	
35	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	..	..	ca	a	a	..	..		
36	Far advanced pulmonary tuberculosis (ca)	.....	a	..	..	c	a	..	..	..		
37	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	..	..	..	a	..	..	a	Tubercles and thrombosis (a)	
38	Cervical Pott's disease	Sinuses (ca)	..	..	..	..	ca	a	..	a	.....	Mitral insufficiency (ca); gallstones (a); mediastinitis (c)
39	Moderately advanced pulmonary tuberculosis, Pott's disease (ca)	Psoas (ca)	..	..	..	..	..	..	..	..	Tuberculous kidney (ca)	Tuberculous prostatitis (a)
40	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	x	..	..	..	a	..	..	Nephrectomy	Operative removal of left testicle
41	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	x	..	..	a	a	..	..	.....	Operative removal of ovary; malacoplakia (a)
42	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	..	..	c	a	..	..	..	Papilloma (a)	Tuberculides (c)
43	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	a	..	..	a	a	..	..		
44	Far advanced pulmonary tuberculosis (ca)	.....	..	a	..	..	a	..	..	..	.....	Terminal hemoptysis (ca); perineal abscess (c)
45	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	..	..	..	..	..	a	a	..	.....	Syphilis of central nervous system (c)
46	Far advanced pulmonary tuberculosis with cavitation; Pott's disease (ca)	Psoas (c)	a	x	c	..	a	..	a	a	Tuberculous kidney (a)	
47	Moderately advanced pulmonary tuberculosis with cavitation (ca)	Empyema (ca)	a	a	..	..	a	ca	..	..	Tubercles (a)	
48	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	x	..	..	a	..	..	a	.....	Carcinoma of sigmoid flexure (a)
49	Far advanced pulmonary tuberculosis (ca)	Empyema (c)	ca	..	ca	..	a	..	..	..	.....	Tuberculous infection of ear (c)
50	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	a	..	..	a	ca	..	..		
51	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	a	..	c	a	..	a	a	Cortical abscess (a)	
52	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	..	..	..	a	a	..	a		
53	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	ca	x	..	..	a	..	..	..		
54	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	..	..	..	a	..	..	..	Hydroureter, hydronephrosis (a)	Multiple peripheral thromboses (c)
55	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	..	a	..	ca	..	..	..		
56	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	..	..	..	..	..	..	..		
57	Far advanced pulmonary tuberculosis with cavitation (ca)	.....	a	..	..	..	a	a	..	a		

* c indicates clinical diagnosis; a, observation at autopsy; ca, clinical diagnosis confirmed at autopsy, and x indicates operative removal of appendix. Amyloid was present in the intestinal wall in cases 4, 7 to 10, 15, 18, 23 and 34.

TABLE 2.—*Clinical Events and Onset of Renal Amyloidosis*

Group	Case	Date	Clinical Event	Date of Presumptive Onset of Amyloidosis	Date of Definite Onset of Amyloidosis
1	1	Dec. 1924	Tuberculous laryngitis	*Aug. 1925	Aug. 1930
		July 1925	*Enteritis		
		Jan. 1928	Ischiorectal abscess that drained		
		Mar. 1928	Enteritis		
	2	Feb. 1927	*Psoas abscess	.....	*Apr. 1927
	3	On admission (Dec. 1926)	Draining tuberculous spine	Dec. 1926	*Oct. 1927
		Sept. 1927	*Abscess closed, aspirated and opened		
	4	June 1930	Hemorrhage	.....	*Aug. 1930
		July 1930	*Left phrenemphraxis; pneumothorax		
	5	May 1930	*Enteritis	.....	*Aug. 1930
	6	On readmission (May 1928)	Draining empyema	May 1928	July 1928
	7	On admission (Oct. 1930)	*Empyema	*Nov. 1930	Jan. 1931
	8	Aug. 1930	*Enteritis	.....	*Sept. 1930
	9	Oct. 1928	*Enteritis	*Oct. 1928	*Feb. 1929
		Dec. 1928	*Enteritis (second attack)		
	10	Nov. 1929	Hemorrhage	.....	*May 1930
		Feb. 1930	First stage thoracoplasty		
		Mar. 1930	Second stage thoracoplasty		
		May 1930	*Third stage thoracoplasty		
	11	Mar. 1930	Pleural effusion, left	*July 1930	*Dec. 1931
		June 1930	*Purulent pleural effusion, right		
		Dec. 1931	*High fever; extension of tuberculosis		
	12	Mar. 1927	*Enteritis	.....	*Mar. 1927
	13	Dec. 1927	*Pneumothorax	.....	*Feb. 1928
		Jan. 1928	*Fluid, base of left lung		
	14	Oct. 1921	Exercise prohibited	Apr. 1918	*Dec. 1921
		Nov. 1921	*Flare up of tuberculosis		
	15	On admission (July 1923)	Psoas abscess	Apr. 1925	Mar. 1928
		Dec. 1924	Pott's disease		
	16	Sept. 1929	*Extension of tuberculosis	*Sept. 1929	Dec. 1931
		Jan. 1930	Bad teeth; pyorrhea		
		May 1931	Questionable enteritis; slight obstruction		
	17	Jan. 1930	Enteritis continuous to death	Mar. 1933	(Terminal) Apr. 1934
		Feb. 1932	Exacerbation of enteritis		
		Aug. 1932	Empyema		
	18	Sept. 1927	Operation on ischiorectal abscess	.....	Sept. 1928
		Apr. 1928	Furunculosis		
		May 1928	Rise of temperature		
		July 1928	*Spread of pulmonary tuberculosis		
		(Early 1926)	Enteritis began; continuous throughout		
		Apr. 1929	Examination of nasal ulcer		
	19	Nov. 1933	Enteritis	Apr. 1934	
	20	Apr. 1932	Nausea and diarrhea; gradual progressive pulmonary tuberculosis with toxemia	Mar. 1933	June 1933
	21	Dec. 1926	Draining sinus, right lower quadrant; postoperative (appendectomy)	.....	*Dec. 1927
		Aug. 1927	Still draining		
		Dec. 1927	*Empyema		
2	22	July 1924	Definite symptoms of enteritis; draining sinuses	July 1925	Nov. 1925
		Feb. 1925	Alternating constipation and diarrhea		
		July 1925	Enteritis		
	23	Jan. 1932	Multiple sinuses draining	*May 1932	*Aug. 1932
		Apr. 1932	*High temperature		
		Aug. 1932	*Sinus closed in right thigh		
	24	Oct. 1930	Several draining sinuses	May 1932	Sept. 1932
		Sept. 1931	Abscess aspirated		
		May 1932	Heavy drainage from back		
		Aug. 1932	Abdomen distended		
		Sept. 1932	Liver enlarged		
	25	Mar. 1930	Pleural fluid	.....	Feb. 1932
		June 1930	Empyema		
		July 1930	Enteritis (roentgen study)		
		Jan. 1930	Granulations on vocal cords		

* The items so marked are the most important clinical events and dates.

TABLE 2.—*Clinical Events and Onset of Renal Amyloidosis—Continued*

Group	Case	Date	Clinical Event	Date of Presumptive Onset of Amyloidosis	Date of Definite Onset of Amyloidosis
2 (cont.)	26	Apr. 1928	First symptoms of enteritis	Oct. 1928	
		June 1928	Lamp treatment for enteritis		
	27	Nov. 1928	*First symptoms of enteritis	.....	*Nov. 1928
		Dec. 1928	Abdominal pain; diet for enteritis		
	28	Mar. 1929	Enteritis	.....	Apr. 1929
	29	Dec. 1931	Progressive tuberculosis	Mar. 1932	
		Mar. 1932	Liver palpable; tuberculous laryngitis		
	30	Oct. 1930	*Rectal fistula; tuberculous laryngitis	*Oct. 1930	Mar. 1931
	31	1925	Insidious gastrointestinal symptoms ending in peritonitis and enteritis	.....	May 1928
	32	Feb. 1929	Enteritis	June 1929	
	33	Mar. 1930	Enteritis	.....	Oct. 1931
	34	May 1926	Symptoms of enteritis	July 1933	
		Feb. 1927	No roentgen evidence of enteritis		
		Feb. 1933	Diarrhea		
		July 1933	Enteritis; tuberculous laryngitis		
	35	Mar. 1934	*Cramps; *diarrhea; edema of ankles	.....	*Apr. 1934
		Apr. 1934	*Enteritis; tuberculous laryngitis (liver and spleen not palpable)		
	36	Sept. 1924	Tuberculous laryngitis	Apr. 1928	
	37	July 1929	Scrotal abscess (probably not significant)	.....	Nov. 1929
		Dec. 1929	Diarrhea		
	38	Feb. 1927	Progressively weaker	.....	*Jan. 1928
		Nov. 1927	*Diagnosis of cervical Pott's disease		
		Aug. 1928	Draining sinus of neck		
	39	Dec. 1930	Psoas abscess draining	Nov. 1931	
	40	Aug. 1920	Nephrectomy; sinus probably closed	.....	Oct. 1922
		Jan. 1922	Opiates given; history suggests mild gastrointestinal disturbance		
		Mar. 1923	Enteritis		
	41	Oct. 1926	Gastrointestinal symptoms began	*Apr. 1927	Dec. 1927
		Nov. 1926	Pneumonic process		
		Feb. 1927	Treatment suggests *enteritis		
	42	Mar. 1925	Gastrointestinal symptoms		
		Apr. 1925	Enteritis		
	43	Jan. 1928	*Tuberculous laryngitis	*Feb. 1928	*July 1928
		Feb. 1928	*Increased activity of pulmonary tuberculosis with probable secondary infection		
		June 1928	*Enteritis		
		July 1928	Gastrointestinal distress		
		Aug. 1928	Edema of ankles		
	44	Oct. 1926	Perineal abscess	.....	June 1925
	45	.....	Nothing to account for original slight albuminuria (syphilitic treatment with heavy metals)	.....	Aug. 1927
		1927	Nothing to account for increase in albuminuria		
	46	Mar. 1929	Psoas abscess started	*Jan. 1932	
		Dec. 1932	*Rectal abscess		
	47	Mar. 1933	Encapsulated pleural fluid		
	48	May 1926	Abdominal pain		
		Sept. 1926	Appendectomy (tuberculous appendix)		
		Apr. 1927	Abdominal distress		
		Oct. 1927	Nausea; pain in side (complicating carcinoma found at autopsy)		
	49	Feb. 1929	Ischiorectal abscess; stormy postoperative course, with healing later		
		Nov. 1928	Enteritis		
	50	July 1929	Symptoms of enteritis		
		May 1930	Apparently large liver		
	51	Mar. 1931	Diarrhea		
		Apr. 1931	Enteritis		
		Aug. 1931	Severe diarrhea		
	52	Apr. 1931	Gastrointestinal distress		
	53	Feb. 1933	Symptoms and roentgen diagnosis of enteritis		
	54	Oct. 1928	Multiple thromboses		
	55	Mar. 1929	Gastrointestinal distress		
	56	Mar. 1930	Anorexia		
	57	.....	.....		

* The items so marked are the most important clinical events and dates.

of albuminuria was twenty-five months, the median being fifteen months (table 3). Thirty-nine patients had heavy albuminuria (2 plus and over) for an average of fifteen and four-fifths months, the median being six months. The incidence of albuminuria and of heavy albuminuria was 82 and 68 per cent, respectively.

TABLE 3.—*Data on Albuminuria*

Case	Total Duration of Albuminuria, Months	Duration of Heavy Albuminuria, Months	Comments
Group 1			
1	63	2	Albuminuria preceded cylindruria by 30 months
2	12	12	
3	21	3	Albuminuria preceded cylindruria by 9 months
4	12	12	Variable in amount; absent on one occasion
5	16	13	Albuminuria preceded cylindruria by 4 months
6	2 (?)	3 (?)	Tuberculous empyema developed 10 months prior to readmission, which was probably onset of renal complication
7	17	16	Albuminuria preceded cylindruria by 2 months
8	4	4	
9	33	6	Albuminuria preceded cylindruria by 5 months
10	4	4	
11	5	1	Cylindruria preceded albuminuria by 17 months
12	44	44	
13	11	9	
14	171	131	Cylindruria preceded albuminuria by 5 months
15	96	62	Albuminuria preceded cylindruria by 34 months
16	15	15	Cylindruria preceded albuminuria by 25 months
17	22	2	Cylindruria preceded albuminuria by 33 months
18	67	67	
19	8	2	Albumin disappeared 5 months before death
20	21	18	
21	15	15	
Group 2			
22	52	7	Few casts
23	1	1	Cylindruria preceded albuminuria by 3 months
24	0	0	Cylindruria 5 months before death
25	34	2	Albuminuria preceded cylindruria by 3 months
26	3	3	No casts
27	2	2	
28	24	5	Albuminuria preceded cylindruria by 19 months
29	8	6	No casts
30	8	0	
31	1	1	Cylindruria preceded albuminuria by 6 months
32	1	0	
33	1	1	
34	1	0	
35	1	1	
36	13	0	
37	1	1	
38	21	18	
39	7	1	No casts
40	102	63	Cylindruria accompanied heavy albuminuria for first 20 months
41	15	9	Casts in last month only
42	36	0	Faint trace of albumin three times; no casts
43	9	7	Albuminuria preceded cylindruria by 2 months
44	41	35	Albuminuria preceded cylindruria by 3 months
45	48	13	Albuminuria preceded cylindruria by 35 months
46	30	0	Albuminuria preceded cylindruria by 3 months
47	0	0	No albumin or casts
48	36	0	Trace of albumin 4 times; no casts
49	18	0	Trace of albumin once; no casts
50	0	0	No albumin or casts
51	0	0	No albumin or casts
52	0	0	No albumin or casts
53	0	0	No albumin or casts
54	0	0	No albumin or casts
55	0	0	No albumin or casts
56	0	0	No albumin or casts
57	0	0	No albumin or casts
Average	25.4	15.8	
Median	15	6	

CYLINDRURIA

Fifteen patients showed no cylindruria, 11 only light cylindruria and 31 heavy cylindruria (table 4). The average total duration of the cylindruria in 42 cases was twenty-one and one-half months, the median

TABLE 4.—*Data on Urinary Sediment*

	Case	Duration of Light Cylindruria (Few to 1+), Months	Duration of Heavy Cylindruria (2 to 4+), Months	Variety of Cast: Hyaline	Variety of Cast: Granular	Leukocytes	Erythrocytes
Group 1							
	1	30	2	+++	±	1-4+	0
	2	12	7	++	+	±	0
	3	12	12	++	+	±	+
	4	12	12	++	±	1+	0
	5	13	11	+++	+	±	0
	6	1	1	++++	0	1-4+	0
	7	15	15	0	+++	4+	+
	8	4	4	++++	0	±	0
	9	28	9	+++	±	±	0
	10	4	1	+	+	±	Once*
	11	22	21	+++	±	±	Once†
	12	44	39	+++	±	±	0
	13	11	11	++++	++	±	0
	14	176	168	++++	++	2+	+
	15	62	42	++++	±	3+	+
	16	40	36	+++	±	1+	+
	17	17	1	+++	+	+	+
	18	67	63	++++	+	±	+
	19	5	3	++++	+	++++	+
	20	21	18	++++	+	+	+
	21	15	6	++	±	+	0
Group 2							
	22	51	0	+	±	+++	Once*
	23	4	1	+++	+	+	0
	24	5	0	+	±	±	0
	25	32	2	+++	±	++	±
	26	0	0	0	0	+++	0
	27	2	2	++	+	++	0
	28	5	0	+	+	+	0
	29	0	0	0	0	++	0
	30	8	3	++++	+	+	0
	31	6	>1	++++	0	+	0
	32	1	0	0	+	+	0
	33	1	>1	++++	+	±	0
	34	>1	0	0	±	+	0
	35	1	1	+++	+++	±	±
	36	1	0	+	0	+	+
	37	1	0	+	±	+	0
	38	21	0	+	±	++++	0
	39	0	0	0	0	++++	++
	40	63	63	++++	++	+	+
	41	1	0	++	+	++	Once*
	42	0	0	0	0	++++	0
	43	7	7 (once)	+++	0	+++	+
	44	38	38	++++	+++	++++	0
	45	13	0	+	0	++++	0
	46	30	0	+	0	±	0
	47	0	0	0	0	±	0
	48	0	0	0	0	±	0
	49	0	0	0	0	+	0
	50	0	0	0	0	±	±
	51	0	0	0	0	±	0
	52	0	0	0	0	±	0
	53	0	0	0	0	±	0
	54	0	0	0	0	+	0
	55	0	0	0	0	+	0
	56	0	0	0	0		
	57	0	0	0	0	±	+
	Average	21.5	19.3				
	Median	12	7				

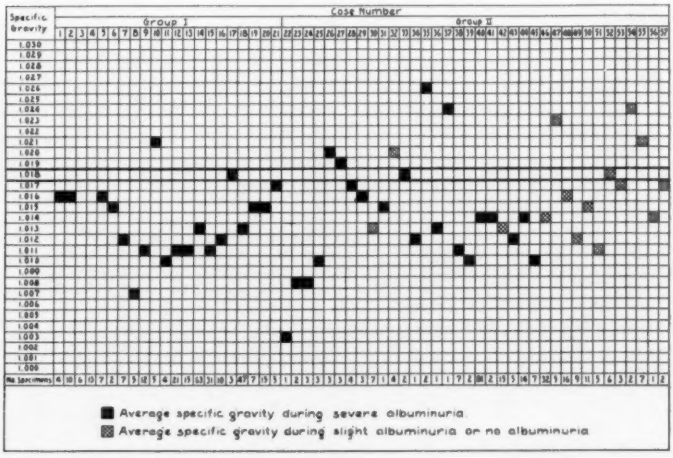
* Three months before death.
† Terminal.

being twelve months. The average total duration of heavy cylindruria in 31 cases was nineteen and three-tenths months, the median being seven months.

Albuminuria appeared first in 12 cases, and cylindruria preceded albuminuria in 6. Six patients with albuminuria showed no casts, 3 of them having heavy albuminuria.

SPECIFIC GRAVITY

As explained in the preceding publication, we arrived at the figure 1.018 as the normal specific gravity for night urine of patients under sanatorium conditions. We also stated that the most constant and



The average specific gravity of the urine in individual cases.

outstanding finding in renal amyloidosis was the low specific gravity of the urine. Only 1 of the 16 patients previously reported on retained the ability to secrete urine that had a normal or above normal specific gravity. In the added cases, even though the clinical features were not as outstanding and albuminuria was frequently absent, a low specific gravity was present in 30 of the 41 patients, or 73 per cent. A low specific gravity was present in 45, or 79 per cent, of the entire series of patients (see the accompanying chart).

FUNCTION OF THE KIDNEYS

Twelve patients were examined by means of the Volhard secretion and concentration test, as shown in table 5. Three showed a normal four hour output (80 per cent or above). Six showed normal dilution

TABLE 5.—*Results of Renal Function Tests*

Case	Volhard Test			Output of Phenolsulfonphthalein in 2 Hours and 10 Minutes		Nonprotein Test for Nitrogen	
	Total 4 Hour Output, %	Maximum Dilution	Maximum Concentration*	Percentage	Time Before Death	Mg. per 100 Cc.	Time Before Death
Group 1							
1	..	.....	.....	....	.....	33	1 mo.
2	52	1.002	1.014	79.0	2 mo.	24 35 24	2 mo. 1½ mo. ½ mo.
3	..	.....	.....	....	.....	..	.....
4	..	.....	.....	....	.....	28	9 mo.
5	..	.....	.....	....	.....	31	½ mo.
6	..	.....	.....	45.0	1 wk.	33	1 wk.
7	..	.....	.....	40.0	14 mo.	34 31	14 mo. 9 mo.
8	50	1.002	1.012	47.5	2½ mo.	27	1½ mo.
9	..	.....	.....	....	.....	29	3 mo.
10	..	.....	.....	....	.....	43	5 yr.
11	..	.....	.....	40.0	9 mo.	31	16 mo.
12	..	.....	.....	....	.....	39 160 174	2 yr. 4 days 1 day
13	50 95	1.004 1.007	1.012 1.014	57.5 37.5	8 mo. 5 mo.	29 36 46	8 mo. 2 mo. 1 mo.
14	64 49	1.002 1.003	1.021 1.017	45.0 40.0	4½ yr. 2 yr. 10 mo.	33 34 33 60 50	6 yr. 10 mo. 4 yr. 2 yr. 10 mo. 10 mo. 7 mo.
15	72	1.005	1.010	22.0	3 yr.	41 72	39 mo. 10 days
16	42	1.005	1.022	45.0	34 mo.	32	34 mo.
17	88	1.001	1.028	59.0	16 mo.	28	16 mo.
18	82	1.001	1.018	50.0 75.0	48 mo. 12 mo.	33 46	48 mo. 12 mo.
19	..	.....	.....	58.0 77.0	13 mo. 7 mo.	31	13 mo.
20	59	1.000	1.027	85.0	10 mo.	30	13 mo.
21	71	1.003	1.024	55.0	5 mo.	28	5 mo.
Group 2							
22	..	.....	.....	42.0 62.0	39 mo. 25 mo.	41	8 mo.
25	..	.....	.....	67.0	21 mo.	34 27	21 mo. 1 mo.
26	..	.....	.....	55.0	2 mo.	28	1 mo.
28	..	.....	.....	66.0	8 mo.	36	8 mo.
38	15	1.005	1.012	22.0	16 mo.	..	.....
39	..	.....	.....	....	.....	34	6 mo.
40	..	.....	.....	24.0 0 0	52 mo. 2 mo. 2 mo.	27† 76 126	55 mo. 2 mo. 4 days
41	..	.....	.....	60.0	15 mo.	33	15 mo.
43	..	.....	.....	....	.....	27	7 mo.
44	27	1.011	1.014	27.0	6 mo.	..	.....
45	..	.....	.....	....	.....	115	1 day
48	..	.....	.....	65.0	17 mo.	..	.....
Normal	80-100	1.001-1.002	1.028-1.032	55-70		30-35	

* Concentrations of from 1.020 to 1.026 indicate moderate impairment; those from 1.010 to 1.020, marked impairment.

† The urea nitrogen content of the blood was 13.6 mg. per hundred cubic centimeters.

(1.002 or below), and only 1 had normal concentration (1.028 or above). Five showed a marked reduction in initial output (50 per cent or less).

Twenty-four patients were given the standard two hour and ten minute intramuscular phenolsulfonphthalein test, and 12 of these had a normal output (55 per cent or above). In case 18 the test was repeated three years after the initial examination, and the output had dropped from 50 to 7.5 per cent. Seven patients showed a moderate impairment of dye excretion (20 to 40 per cent output), and only 2 showed marked impairment (cases 18 and 40, with 7.5 and 0 per cent, respectively).

Of 29 patients for whom the nonprotein nitrogen content of the blood was determined, 5 showed a significant degree of nitrogen retention (50 mg. or more per hundred cubic centimeters), 4 showed slight retention (40 to 50 mg.) and 20 showed readings that were normal (below 40 mg.). However, in 13 instances the determination was made more than three months before death, so it is possible that some of these patients had terminal nitrogen retention.

BLOOD PRESSURE

As shown in table 6, for 47 patients the blood pressure was determined on entry. Six of these patients (cases 13, 16, 24, 29, 31 and 47) showed a systolic reading of 130 mm. or above. In case 17 the blood pressure was elevated after entry and forty months before death. Hypotension was a frequent finding. However, low blood pressure readings are common among our patients at the sanatorium. For 28 patients, one to several determinations of the blood pressure were made after the onset of presumptive or definite renal amyloidosis. In 10 of these patients (cases 11 to 16, 18, 29, 44 and 47) there was elevation of the blood pressure (a systolic pressure of 130 mm. or above), and 5 of them (cases 12 to 16) showed arteriolosclerosis of the kidney. One patient (case 31) who had an elevated blood pressure on entry showed renal arteriolosclerosis. Seven patients (cases 19, 25, 27, 33, 36, 38 and 42) showed some degree of renal arteriolosclerosis with a normal or low blood pressure, but for 5 patients (cases 25, 33, 36, 38 and 42) the blood pressure determinations were obtained one year or more before death. One patient (case 45) had renal arteriolosclerosis, but no determination of the blood pressure was made. One patient (case 12) showed a moderate grade of hypertension while under observation for renal amyloidosis. He had marked nitrogen retention. At postmortem examination the kidneys showed arteriolosclerosis and chronic nephritis. In case 13 the condition may be termed latent hyper-

TABLE 6.—*Data on Blood Pressure*

	Case	Date of Death	Admission		During Residence		Final Reading		
			Date	Blood Pressure, Mm. of Mercury	Date	Blood Pressure, Mm. of Mercury	Date	Blood Pressure, Mm. of Mercury	Time Before Death
Group 1									
	1	9/ 3/30	12/ 5/24	100/66	.....	.....	Aug. 1930	104/ 70	1 mo.
	2	4/ 2/28	7/ 2/25	.....	7/ 9/27	100/ 60	3/29/28	70/ 50	4 days
					3/19/28	104/ 90			
	3	9/11/28	12/31/26	104/64	.....	.....	July 1928	100/ 66	2 mo.
	4	7/ 8/31	12/ 8/29	108/72	Sept. 1930	102/ 62	10/30/30	90/ 70	9 mo.
	5	8/ 4/31	8/13/26	108/48	.....	.....	11/ 7/30	104/ 64	9 mo.
			6/ 7/29	106/50					
	6	7/27/28	5/18/28	125/78	.....	.....	7/26/28	100/ 60	1 day
	7	3/10/32	10/22/30	95/70	.....	.....	3/28/31	102/ 68	11½ mo.
	8	1/17/31	8/21/29	102/66	10/18/30	102/ 74	11/13/30	108/ 80	2 mo.
	9	5/ 1/31	6/ 4/28	110/85	.....	.....	1/24/31	108/ 65	3 mo.
	10	8/29/30	2/27/18	.....	4/23/24	110/ 80	5/15/30	118/ 80	3 mo.
	11	4/ 9/32	11/21/29	120/72	9/ 6/30	138/100	11/13/30	116/ 92	16 mo.
	12	10/10/30	8/30/24	118/74	10/18/28	136/ 80	4/10/30	174/ 92	6 mo.
					7/19/29	142/ 82			
	13	12/26/28	12/26/25	148/90	1/ 1/26	125/ 90	11/22/28	135/ 94	1 mo.
	14	10/12/32	4/10/17	.....	1/ 3/22	130/ 80	5/29/32	194/120	5 mo.
					12/29/25	140/ 98			
					10/18/28	228/122			
	15	3/24/33	7/25/23	108/80	1/ 1/26	125/ 67	3/ 9/33	108/ 62	½ mo.
			12/12/24	106/75	10/10/28	120/ 78			
					2/ 4/30	150/ 90			
					12/ 6/32	136/ 74			
	16	12/ 4/32	7/20/29	140/88	2/ 4/30	162/110	11/24/32	178/120	½ mo.
	17	7/ 1/34	3/25/29	112/82	.....	.....	3/31/31	136/104	40 mo.
	18	3/18/34	2/17/26	102/66	4/ 7/30	102/ 70	2/ 2/33	132/ 94	13 mo.
	19	8/14/34	7/ 1/31	104/72	.....	.....	4/19/34	108/ 70	4 mo.
	20	12/20/34	5/29/27	110/70	.....	.....	11/ 1/34	104/ 76	1 mo.
	21	3/ 7/29	4/13/27	.....	Aug. 1928	112/ 80	.....	.....	8 mo.
Group 2									
	22	11/17/29	1/16/23	98/64	.....	.....	.....	.....	7 yr.
	23	9/26/32	1/28/32	112/65	.....	.....	.....	.....	8 mo.
	24	11/ 2/32	10/15/30	134/92	.....	.....	.....	.....	2 yr.
	25	4/ 2/32	10/26/28	110/80	.....	.....	.....	.....	5½ yr.
	26	1/ 7/29	11/ 2/27	100/20	.....	.....	.....	.....	1 yr.
	27	1/11/29	11/ 6/28	92/60	.....	.....	.....	.....	2 mo.
	28	9/ 2/29	9/ 6/27	92/64	.....	.....	.....	.....	2 yr.
	29	11/24/32	11/25/27	140/92	.....	.....	3/18/32	148/ 86	8 mo.
	30	6/ 9/31	10/22/30	116/80	.....	.....	.....	.....	8 mo.
	31	5/29/28	11/23/27	136/82	.....	.....	.....	.....	6 mo.
	32	7/ 2/29	10/ 3/28	.....	.....	.....	.....	.....	.....
	33	11/24/31	6/29/29	124/80	.....	.....	.....	.....	29 mo.
	34	7/27/33	4/ 5/24	.....	5/ 1/28	135/ 95	7/13/33	90/ 76	14 days
	35	5/ 4/34	4/25/34	98/66	.....	.....	.....	.....	9 days
	36	5/12/28	9/11/24	.....	1/16/26	88/ 48	.....	.....	2 yr.
	37	12/30/29	1/12/29	116/74	.....	.....	.....	.....	11 mo.
	38	6/11/29	6/24/18	.....	8/ 6/27	100/ 48	6/19/28	104/ 52	12 mo.
	39	12/22/31	5/ 2/31	122/78	.....	.....	.....	.....	7 mo.
	40	12/20/27	6/10/19	.....	11/20/27	90/ 62	12/17/27	68/ 38	3 days
	41	1/17/28	10/10/26	.....	.....	.....	.....	.....	.....
	42	6/24/28	7/12/24	115/65	.....	.....	.....	.....	4 yr.
	43	9/26/28	1/29/28	90/72	.....	.....	.....	.....	8 mo.
	44	8/26/28	10/30/24	.....	12/29/25	148/100	.....	.....	2½ yr.
	45	9/28/28	6/20/22	.....	.....	.....	.....	.....	.....
	46	6/22/34	12/10/27	120/88	.....	.....	.....	.....	6½ yr.
	47	2/21/34	3/ 9/33	155/90	.....	.....	.....	.....	11 mo.
	48	4/17/29	1/18/26	124/92	.....	.....	.....	.....	3 yr.
	49	8/26/29	9/ 2/27	102/68	.....	.....	.....	.....	2 yr.
	50	7/12/30	6/18/28	102/70	.....	.....	.....	.....	2 yr.
	51	9/14/31	11/19/30	110/80	.....	.....	.....	.....	10 mo.
	52	1/ 2/32	10/25/30	110/72	.....	.....	.....	.....	1 yr.
	53	3/17/33	9/ 7/32	118/78	.....	.....	.....	.....	6 mo.
	54	12/28/28	9/ 6/28	92/65	.....	.....	.....	.....	3 mo.
	55	8/24/29	2/ 7/28	108/70	.....	.....	.....	.....	1½ yr.
	56	7/13/30	7/ 9/30	92/46	.....	.....	.....	.....	4 days
	57	1/29/32	11/24/31	118/74	.....	.....	.....	.....	2 mo.

tension. Renal amyloidosis did not appear to influence his blood pressure. He showed a slight elevation of the nonprotein nitrogen level one month before death. At postmortem examination the glomerular lesion of chronic nephritis was present. In case 14 there was marked and prolonged hypertension, the first evidence of which occurred four years after the onset of renal amyloidosis. Because of the high blood pressure and the good renal function as regards the elimination of nitrogen during the period from eight to three years before death, we considered it highly probable that this patient had two conditions—renal amyloidosis and primary arterial hypertension. At postmortem examination, marked arteriosclerosis and arteriolosclerosis and chronic nephritis were present. In case 15 there was a slight degree of hypertension after the onset of renal amyloidosis. The blood pressure became subnormal two weeks before death. Postmortem examination showed arteriolosclerosis and chronic nephritis. In case 16 there was a slight elevation of the blood pressure on entry. Moderate hypertension developed. At postmortem examination arteriolosclerosis and chronic nephritis were present. In cases 11, 17, 18, 29, 44 and 47 there were minimal increases in the blood pressure at some time during residence, without evidence of arteriolosclerosis, but in case 44 there was marked arteriosclerosis of the larger renal arteries.

Of the 13 patients showing an elevated blood pressure at some time during residence, 12 were men, aged 21, 32, 33, 39, 45, 46, 53, 56, 57, 57, 58 and 72 years, respectively, and 1 was a woman, aged 26 years.

One patient (case 40) was noteworthy in that he had had one kidney removed. He showed marked albuminuria and cylindruria, with the phenolsulfonphthalein excretion diminishing to zero and with marked retention of nitrogen. His blood pressure was low one month and also three days before death. The eyegrounds showed no evidence of arteriolosclerosis or retinitis at the time of the last two determinations of the blood pressure. This patient is cited as one who had an ample basis for "albuminuric retinitis" if the kidney alone were able to produce it independent of degenerative vascular changes in the retina. This patient's condition in some respects was comparable to that in Anderson's [2] experimental animals. Anderson removed about three fourths of the total renal tissue from rabbits and thereby produced a marked degree of nitrogen retention without causing either hypertension or retinitis.

From the evidence presented it appears that hypertension occupies an inconspicuous position in the clinical picture of renal amyloidosis. It may be incidental rather than related to cause and effect.

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2. Anderson, H. C.: The Relation of Blood Pressure to the Amount of Renal Tissue, J. Exper. Med. **39**:707 (May) 1924.

EXAMINATION OF EYEGROUNDS

In 19 cases an examination of the eyegrounds was made. In 11 (cases 1, 2, 4 to 9, 18, 19 and 40) the disks and retinas were normal, and there were no detectable vascular changes. In case 3 there was slight variation in the lumen of one inferior temporal artery. In case 13 one inferior temporal artery had a burnished appearance, suggesting an early "copper wire artery." In case 15 the arteries showed slight narrowing, and the choroid vessels were slightly prominent. The "pepper and salt" fundus was present in both macular regions. In case 17 one temporal artery had a burnished appearance, suggesting a "copper wire artery." In these 4 patients the vascular changes were so slight that they must be considered questionable. In case 11 the arteries showed slight dulling of the light reflex, with slight narrowing and irregularity of the lumen. We consider these changes indicative of early retinal arteriolosclerosis. In case 12 there were a slight increase in the vascularity of the disks, marked tortuosity of vessels, an increased light reflex (early "copper wire artery") and moderate arteriovenous compression. In case 16 there were a moderately increased light reflex and irregularity of the lumen of the arteries, with slight arteriovenous compression. We consider that these 2 patients showed moderate retinal arteriolosclerosis. In case 14 the arteries showed marked irregularity and narrowing of the lumen. Some were almost obliterated. There was slight compression at several arteriovenous crossings. This patient had marked retinal arteriolosclerosis. All the patients examined were free from retinal hemorrhages and retinitis. It appears from this that the eyegrounds are usually normal in uncomplicated renal amyloidosis.

PHYSICAL FINDINGS

Twenty patients had a special physical examination, which was usually made within one to three months after the onset of renal amyloidosis. The findings are shown in table 7. In the case of other patients not examined by us we are utilizing the bedside notes of the attending physician in establishing the presence of edema and enlargement of the liver. Slight to moderate pallor was noted in 13 patients. Slight to marked clinical edema was noted in 14 patients. In 8 it was slight, and in the remaining 6 it was of moderate to marked degree. In half the patients it was apparent only in the feet and legs. Edema, as noted at postmortem examination, was general in 10 instances. In 7 of these it was of slight to moderate degree. Localized edema, usually in the feet alone or in the hands and feet, was present in 31 cases, and in all but 2 cases it was of slight to moderate degree. Simon [3] found edema in 14 of 45 patients, and initial edema was present

3. Simon, S.: Zur Klinik der Nephrose bei Knochen- und Gelenktuberkulose, Deutsches Arch. f. klin. Med. **163**:87, 1929.

TABLE 7.—*Physical Findings and Postmortem Weights*

	Case	Sex	Age at Death, Yr.	Pallor	Edema		Peripheral Arteriosclerosis	Liver		Spleen		Heart: Postmortem Weight, Gm.	Physical Examination, Months Before Death
					Grade	Location		Cm. Below Costal Margin	Postmortem Weight, Gm.	Cm. Below Costal Margin	Postmortem Weight, Gm.		
Group 1													
	1	F	33	2+	1+	Ankles; legs	3+	Enlarged	1,560	Enlarged	270	230	2
	2	M	26	2+	3+	Legs; abdomen	1+	Not palpable	2,015	Not palpable	214	212	1
	3	M	33	2+	0	.....	0	3.0	3,405	0	475	210	4
	4	F	25	0	0	.....	0	0	2,666	0	340	146	12
	5	M	28	2+	0	.....	2+	8.0	3,070	0	246	163	10
	6	F	23	1+	0	.....	0	5.0	3,950	2	524	405	1
	7	F	20	2+	2+	Face	3+	3.5	2,440	2	650	155	13
	8	F	27	1+	0	.....	0	3	2,730	0	245	160	3
	9	F	42	2+	0	.....	0	8	2,835	6	300	197	6
	10	M	35	...	...	.....	...	...	1,450	..	206	417	..
	11	M	33	0	0	.....	3+	0	2,325	0	268	228	20
	12	M	56	0	0	.....	2+	0	1,967	0	108	588	7
	13	M	45	0	0	.....	3+	0	1,200	0	240	297	2
	14	M	53	2+	2+ 3+	Face; legs	3+	0	1,902	0	215	457	6
	15	M	58	2+	1+	Legs	2+	0	2,800	4	543	335	42
	16	M	72	0	0	.....	2+	0	2,085	2	260	580	34
	17	M	39	2	...	Ankles	2+	...	1,400	3	330	243	16
	18	M	32	0	...	.....	2+	4.5	3,017	0	331	315	13
	19	F	33	3	...	Feet; ankles; leg; hand	...	Not palpable	1,520	Not palpable	180	160	4
	20	F	29	3	0	Ankles	2+	6.0	2,648	Not palpable	176	281	1
	21	M	30	...	...	.....	...	...	1,654	..	300	...	..
Group 2													
	22	M	39	...	...	.....	...	...	2,430	..	345	360	..
	23	F	19	...	...	Ankles; hand	...	...	1,275	..	225	95	..
	24	M	21	...	...	.....	...	...	1,885	..	485	109	..

25	F	43	...	...	General	...	...	1,560	..	210	185	..
26	F	19	...	...	Ankles	...	...	1,805	..	179	174	..
27	M	68	...	...	.....	...	...	1,240	..	240	270	..
28	F	29	...	...	Ankles	...	...	1,500	..	175	140	..
29	F	26	...	...	Ankles; wrists	...	...	1,534	..	250	175	..
30	F	28	...	...	.....	...	...	1,375	..	170	175	..
31	M	46	...	...	Ankles	...	...	2,360	..	345	254	..
32	M	27	...	...	Feet	...	...	2,185	..	265	225	..
33	M	46	...	...	.....	...	...	1,587	..	205	212	..
34	F	35	...	...	.....	...	...	2,410	..	317	213	..
35	M	39	...	...	Ankles; hand	...	...	1,570	..	140	240	..
36	F	62	...	...	Ankles	...	...	1,145	..	208	300	..
37	M	24	...	...	Legs	...	...	1,870	..	280	210	..
38	F	41	...	...	General	...	...	1,050	..	194	246	..
39	M	32	...	...	.....	...	...	1,155	..	165	147	..
40	M	36	...	...	.....	...	...	.....	..	...	...	..
41	F	42	...	...	.....	...	...	1,965	..	145	310	..
42	M	54	...	...	.....	...	...	.....	..	...	...	..
43	F	28	...	...	Ankles	...	...	1,335	..	176	176	..
44	M	57	...	...	.....	...	...	1,710	..	150	322	..
45	F	47	...	...	.....	...	...	1,210	..	193	...	..
46	M	33	...	...	Feet; hands; ankles	...	...	3,290	..	420	240	..
47	M	57	...	...	.....	...	...	2,370	..	605	350	..
48	M	61	...	...	Feet; ankles	...	...	1,815	..	174	270	..
49	F	20	...	...	Ankles	...	...	1,850	..	115	125	..
50	M	29	...	...	Hands; ankles	...	...	2,806	..	215	252	..
51	F	22	...	...	Ankles	...	...	1,911	..	322	165	..
52	M	44	...	...	Ankles	...	...	1,460	..	200	210	..
53	F	32	...	...	Feet; ankles	...	...	1,340	..	290	198	..
54	F	48	...	...	Ankles	...	...	1,026	..	185	175	..
55	M	36	...	...	Ankles	...	...	1,300	..	60	250	..
56	M	71	...	...	.....	...	...	1,465	..	202	295	..
57	M	23	...	...	.....	...	...	1,525	..	363	332	..
Average								1,926.4		266.7		
Average in previous series of cases								2,337.5		320.7		

in 6 of 30 patients observed from the beginning. He stated that in a large number of patients no edema except terminal edema was present. Holten [4] stated that initial edema, as seen in ordinary nephritis, is not present. In 13 of his 30 patients there was no edema, and in only 3 was edema present that was not terminal. Our observations that the initial edema of ordinary nephritis is not present in renal amyloidosis agrees with Holten's observations. When edema is present in the early stage, its onset is more insidious. It will be approximately correct to say that one fourth of the patients with renal amyloid have edema at some time during the early and middle periods of the disease, while two thirds have terminal edema. One of our patients (case 12) had marked albuminuria for four years and at postmortem examination showed only slight generalized edema. Another patient (case 13) had severe albuminuria for nine months and no edema. We do not find any agreement in the amount of albuminuria and edema in our series. The condition is probably due to other factors than depletion of plasma protein by loss of albumin.

The clinical estimates of the enlargement of the liver and spleen together with postmortem weights are given in table 7. In 11 cases in which an examination was made less than six months before death, the examiner's estimate of the size of the liver and spleen was approximately correct when compared with the postmortem data. We assume that a 25 per cent increase in the size of the liver and an 80 per cent increase in the size of the spleen are necessary before enlargement of these organs can be demonstrated by physical diagnostic methods. These figures correspond closely with the standards of Barron and Litman,[5] who stated that a liver weighing 2,200 Gm. or more and a spleen weighing 300 Gm. or more are enlarged sufficiently to be demonstrable by palpation. These approximate the figures we used, namely, 2,250 Gm. and 1,875 Gm., respectively, for the weight of the liver and 270 Gm. for the weight of the spleen in either sex. We used as a basis for calculation 1,800 Gm. as the normal weight of the liver in men and 1,500 Gm. as the normal weight in women and 150 Gm. as the normal weight of the spleen in either men or women. These figures closely approximate the normal figures given by Boyd.[6] In 13 of 31 men the weight of the liver was not increased (1,800 Gm. or less). In 2 cases the postmortem examination was not made at the sanatorium, and we are not using the weights reported. In 9 of 24 women the weight of the liver was not increased (1,500 Gm. or less).

4. Holten, C.: Nephritis Caused by Tuberculosis, Acta med. Scandinav. **61**: 107, 1924.

5. Barron, M., and Litman, A. B.: Importance of Hepatomegaly and Splenomegaly in Differential Diagnosis, Arch. Int. Med. **50**:240 (Aug.) 1932.

6. Boyd, E.: Normal Variability in Weight of the Adult Human Liver and Spleen, Arch. Path. **16**:350 (Sept.) 1933.

On the basis of the postmortem weight there was enlargement of the liver in 60 per cent of the cases. If it is assumed that the weight of the liver must increase 25 per cent before enlargement can be demonstrated by physical examination (2,250 Gm. in men and 1,875 Gm. in women), in only 10 men and 9 women were these levels reached (34.5 per cent). If enlargement of the liver that was demonstrable by physical examination had been made a diagnostic requirement in this series, the diagnostic error would have been 65.5 per cent.

In 4 of 31 men and in 2 of 24 women the weight of the spleen (150 Gm.) was not increased. The incidence of enlargement of the spleen on the basis of the postmortem weight was 89 per cent. If it is assumed that an 80 per cent increase in the size of the organ is necessary before enlargement can be demonstrated by physical examination, it is found that enlargement was present in 28 cases, or 59 per cent. Thus, if demonstrable enlargement of the spleen had been made a diagnostic requirement, the diagnostic error would have been 41 per cent. If the usual textbook diagnostic triad of chronic suppuration, enlargement of the liver and spleen and albuminuria had been insisted on, the diagnostic error would have been 89 per cent. Cases 3, 6, 7, 9, 22 and 31 are the only ones in which these requirements were met.

The congo red test, according to the technic of Bennhold,[7] was performed on 7 patients (cases 6, 8, 9, 11, 14, 15 and 18). The percentage of disappearance of the dye was 100, 40, 39, 90, 90, 100 and 100, respectively. In cases 8 and 11, with a disappearance of 40 and 39 per cent, respectively (in the doubtful range), there was enlargement of both liver and spleen; while in case 14, with 90 per cent disappearance, there was only slight enlargement of the liver and spleen. While the congo red test is helpful in the diagnosis of amyloidosis, our experience in this series of cases and in others leads us to believe that there is too great variability of response to make it a dependable diagnostic test on which to base an early diagnosis.[8] We performed the test only in

7. Bennhold, H.: Ueber die Ausscheidung intravenös einverleibten Kongorotes bei den verschiedensten Erkrankungen insbesondere bei Amyloidosis, Deutsches Arch. f. klin. Med. **143**:32, 1923.

8. Since the preparation of this manuscript there has been published by S. Lipstein an evaluation of the congo red test for amyloidosis (Am. J. M. Sc. **195**: 205, 1938), in which he has made the following statement. "The congo red test can be interpreted only as confirmatory evidence of amyloid disease when the percentage of dye absorption is 90 per cent or higher." In the absence of amyloidosis in 91 tuberculous patients, he found the dye absorption to be from 10 to 75 per cent in all instances, with 4 exceptions in which values of 80, 90, 95, and 100 per cent, respectively, were recorded. In 34 cases of amyloidosis observed at postmortem examination, the absorption values were from 90 to 100 per cent in all but 5 cases, the exceptions being values of 82, 60, 35, 35 and 35 per cent.

TABLE 8.—*Diagnostic Scheme* *

Case	Point 1			Point 2		Point 3		Point 4			Contrary Urinary Findings		Comment
	Suppurating Focus	Clinical Enteritis	Tuberculosis of Serous Membrane	Albuminuria	Cylindruria	Enlarged Liver	Enlarged Spleen	Specific Gravity of 1.015 or Below	Diagnostic Score, Points	Postmortem Renal Amyloidosis	Pyuria	Hematuria	
Group 1													
1	0	+	0	+	+	0	+	0	3	A	+	0	
2	+	0	+	+	+	0	0	0	2	A	0	0	Suppurating focus and albuminuria sufficient for diagnosis
3	+	0	0	+	+	+	+	+	4	A	0	+	
4	0	+	0	+	+	+	+	+	4	A	0	0	
5	0	+	0	+	+	+	0	0	3	A	0	0	
6	+	0	+	+	+	+	+	+	4	A	+	0	
7	+	0	0	+	+	+	+	+	4	A	+	+	
8	0	+	0	+	+	+	0	+	4	A	0	0	
9	0	+	0	+	+	+	+	+	4	A	0	0	
10	0	+	0	+	+	0	0	0	2	A	0	0	Diagnosis made on basis of enteritis and urinary findings
11	+	+	+	+	+	+	+	+	4	A	0	0	
12	0	+	0	+	+	0	0	+	3	A	0	0	
13	0	0	0	+	+	0	0	+	2	A	0	0	Probably not sufficient evidence for diagnosis even though correct
14	0	+	+	+	+	+	+	+	4	A	+	+	
15	+	+	0	+	+	+	0	+	4	A	+	+	
16	0	0	0	+	+	+	+	+	3	A	0	+	
17	+	+	+	+	+	0	+	0	3	A	0	+	
18	0	+	0	+	+	+	+	+	4	A	0	+	
19	0	+	0	+	+	0	0	+	3	a	+	+	Enteritis and albuminuria sufficient for diagnosis
20	0	+	+	+	+	+	0	+	4	A	0	+	
21	+	+	+	+	+	0	+	0	3	A	0	0	
Group 2													
22	+	+	0	+	0	+	+	+	4	A	+	0	Meager urinary findings at time of study; poor follow-up study; missed case; diagnosis should have been amyloid kidney
23	+	0	0	+	+	0	0	+	3	A	0	0	Terminal case; meager urinary findings until last month; amyloid kidney should have been suspected before death; edema was present
24	+	0	0	0	0	0	+	+	3	A	0	0	Falling specific gravity; occasional casts; amyloid kidney should have been suspected; careful physical examination would have revealed large spleen
25	+	+	+	+	+	0	0	+	3	A	+	0	Urinary findings meager until terminal stage; amyloid kidney should have been suspected
26	0	+	0	+	0	0	0	0	2	A	+	0	Amyloid kidney should have been suspected 3 months before death

27	0	+	0	+	+	0	0	0	2	A	+	0	Amyloid kidney should have been diagnosed because of combination of enteritis and heavy albuminuria
28	0	+	0	+	+	0	0	0	2	A	0	0	Amyloid kidney should have been diagnosed because of combination of enteritis and heavy albuminuria
29	0	0	0	+	0	0	0	0	1	A	+	0	Only reason for suspecting amyloid kidney, increasing albuminuria in last 5 months of life
30	0	0	0	+	+	0	0	+	2	A	0	0	Amyloid kidney should have been suspected from urinary findings
31	+	+	+	+	+	+	+	+	4	A	0	0	Amyloid kidney should have been diagnosed; missed because albuminuria appeared late
32	0	+	0	+	+	0	0	0	2	A	0	0	Meager urinary findings until terminal stage; amyloid kidney might have been suspected because of enteritis and albuminuria
33	0	+	0	+	+	0	0	0	2	A	0	0	Terminal evidence only, but amyloid kidney should have been suspected because of enteritis and heavy albuminuria
34	0	+	0	+	+	+	+	+	4	A	0	0	Meager urinary findings and terminal only, but diagnosis should have been made or at least strongly suspected because of enteritis, enlarged liver and spleen
35	0	+	0	+	+	0	0	0	2	A	0	0	Terminal evidence only, but amyloid kidney should have been diagnosed because of enteritis and heavy albuminuria
36	0	0	0	+	+	0	0	+	2	A	0	+	Meager urinary findings only; no reason for suspecting amyloidosis
37	0	0	0	+	+	0	+	0	2	A	0	0	Heavy terminal albuminuria only; careful physical examination might have demonstrated enlargement of spleen
38	+	0	0	+	+	0	0	+	3	a	+	0	Should have been diagnosed amyloid kidney; poor follow-up study
39	+	0	0	+	0	0	0	+	3	A	+	+	Amyloid kidney should have been suspected; missed because of absence of casts and presence of pyuria
40	0	0	0	+	+	..	..	+	2	A	+	+	Only one kidney; diagnosis missed because chronic nephritis without hypertension was suspected
41	0	0	0	+	+	+	0	+	3	A	+	0	Diagnosis missed because of inexperience; no casts (except during last month) and pyuria influenced diagnosis
42	0	+	0	0	0	..	..	+	2	A	+	0	Only faint trace of albumin; marked pyuria; little grounds for suspicion
43	0	0	0	+	0	0	0	+	2	A	+	+	Should have been suspected; unduly influenced because of absence of casts and presence of pyuria and hematuria
44	0	0	0	+	+	0	0	+	2	A	+	0	Should have been suspected; influenced by pyuria and few casts; one of first cases studied
45	0	0	0	+	+	0	0	+	2	A	+	0	Should have been diagnosed because of long-continued heavy albuminuria and cylindruria
46	+	0	0	0	0	+	+	+	3	A	0	0	Should have been strongly suspected or even diagnosed
47	+	+	+	0	0	+	+	0	2	A	0	0	Probably should have been diagnosed amyloidosis of liver and spleen
48	0	0	0	0	0	0	0	0	1	A	0	0	No basis for suspicion
49	0	+	0	0	0	0	0	+	1	A	0	0	Enteritis with low specific gravity of urine should have raised suspicion
50	+	+	+	0	0	+	0	0	2	A	0	0	Amyloid disease should have been suspected
51	0	+	0	0	0	0	+	+	3	A	0	0	Amyloid kidney should have been suspected without albuminuria
52	0	+	0	0	0	0	0	0	1	A	0	0	No basis for suspicion
53	0	+	0	0	0	0	+	0	2	A	0	0	Amyloid disease should have been suspected
54	0	0	0	0	0	0	0	0	0	a	0	0	No basis for suspicion
55	0	0	0	0	0	0	0	0	0	a	0	0	No basis for suspicion
56	0	0	0	0	0	0	0	+	1	a	0	0	Low specific gravity of urine was only reason for suspicion
57	0	0	0	0	0	0	+	0	1	a	0	+	Enlarged spleen was only basis for suspicion

* Slight albuminuria and slight cylindruria were not assigned a point value.

cases in which the diagnosis had been made. We admit, however, that in doubtful cases a positive reaction to the congo red test should carry considerable weight. We are now employing this test and obtaining plasma protein determinations in all cases of suspected renal amyloidosis, and we hope to define the usefulness of these procedures in the early diagnosis of amyloid kidney.

COMMENTS ON DIAGNOSIS

We have evolved table 8 on a basis of the clinical findings, and we believe that its use will lead to the discovery of a larger number of cases of amyloid kidney in sanatoriums for patients with tuberculosis. This table is constructed on the basis of a four point diagnosis. From the standpoint of importance we group the suppurating focus, enteritis and tuberculosis of the serous membranes together; if any one of these conditions is present, this counts one point in the diagnosis. Albuminuria accompanied by or in the absence of cylindruria counts a second point. While in no case did cylindruria run its whole course without albuminuria, there are times when cylindruria should be assigned a value in the absence of albuminuria, especially if there is the more or less characteristic sediment with the "one type" hyaline cast with fat droplets, as mentioned in a former publication. In this tabulation we have not designated that albumin was present in the urine unless it occurred with more or less constancy and in significant amount. We have eliminated cases in which there was an occasional or faint trace of albumin or a similar degree of cylindruria, such as conceivably might occur in any patient seriously ill with tuberculosis. Third in importance is enlargement of the liver and spleen. Our criteria for enlargement have previously been mentioned. We employ direct and indirect percussion as well as palpation. The normal extent of dulness of the liver should be approximately 7 and 10 cm. at the midline and at the mammary line respectively; and if these figures are increased by 2 cm., the liver should be considered enlarged. By the same method, the long diameter of the spleen in the normal person is 10.5 cm.; and when it is 12.5 cm. or above, it should be considered enlarged.

The normal specific gravity of the night urine under sanatorium conditions in 200 nonfatal and 80 fatal cases in which there was no renal disease was found to average 1.018. We are taking 1.015 or below as a significant departure from normal. We do not consider that this finding is as important in establishing the diagnosis as the first three that have been mentioned, but it occurs with sufficient frequency (61 per cent) so that it should be given some consideration. Renal function tests of water secretion and concentration and of the

output of dye, determinations of the nonprotein nitrogen content and of the blood pressure, and eyeground examinations have their place in the differential diagnosis of amyloidosis from the other nephropathies. Edema likewise is usually absent when a case comes up for diagnosis.

Referring to table 1, it will be seen that 41 patients (72 per cent) had a suppurating focus, clinical enteritis or tuberculosis of serous membranes or these conditions in combination and that 33 patients also had albuminuria and cylindruria. Both enteritis and albuminuria occurred 25 times (44 per cent), the most frequent association. Enlargement of the liver or spleen or both occurred 28 times (51 per cent).

In reviewing the diagnostic table it is seen that 29 patients (51 per cent) had either a three or four point diagnosis, which we feel was sufficient for a clinical diagnosis of renal amyloidosis. If the patients with a suppurating focus or clinical enteritis who later showed albuminuria are added, the number is increased to 37 (65 per cent); we believe that this is a safe diagnostic practice. It must be taken into account, however, that all these patients had tuberculosis.

PATHOLOGIC EXAMINATION

Other body tissues, in addition to the kidney, were studied for the presence of amyloid. The tissues, in addition to gross examination after the iodine test, were also examined microscopically after hematoxylin and eosin and methyl violet stains had been employed. The distribution of the amyloid observed in the various organs is shown in table 9. In all cases amyloid was present in the kidney and spleen, but in 5 instances it could not be demonstrated in the liver. The adrenal glands, mesenteric lymph nodes, tracheal lymph nodes, small and large intestine, pancreas and thyroid contained amyloid, the amount decreasing in the order named. Our findings are in close accord with those of Rosenblatt.[9]

The weight of the kidneys and the microscopic distribution of amyloid are given in table 10. When the degree and duration of albuminuria and cylindruria are compared with the amount and distribution of amyloid in the kidney, it is possible to make some generalization. The patients with the greatest amount of amyloid in the glomeruli were usually those in whom the albuminuria was most marked and of the longest duration. All the patients with marked albuminuria at some time showed amyloid in the glomeruli, and only 6 of 42 patients with marked albuminuria had a slight amount. The patients with marked albuminuria usually showed a heavy deposit of amyloid also in the other parts of the kidney.

9. Rosenblatt, M. B.: Amyloidosis and Amyloid Nephrosis, Am. J. M. Sc. **86**:558 (Oct.) 1933.

TABLE 9.—*Distribution of Amyloid as Observed Post Mortem* *

Case	Kidney	Liver	Spleen	Pancreas	Adrenals	Mesenteric Lymph Nodes	Retroperitoneal Lymph Nodes	Appendix	Tracheal Lymph Nodes	Thyroid	Small Intestine	Large Intestine
Group 1												
1	A	A	A	—	a	—	0	—	—	0	—	—
2	A	A	A	A	A	A	A	—	—	0	—	—
3	A	A	A	A	A	?	0	A	A	0	—	A
4	A	A	A	A	A	—	0	—	—	—	A	A
5	A	A	A	—	A	A	0	—	—	—	—	—
6	A	A	A	—	A	—	0	—	—	0	—	—
7	A	A	A	—	?	?	—	—	—	—	†	A
8	A	A	A	—	A	—	0	—	—	0	A	0
9	A	A	A	A	A	—	0	A	—	A	—	—
10	A	A	A	—	a	—	0	—	—	0	A	—
11	A	A	A	—	A	A	—	—	?	A	—	—
12	A	A	A	—	A	—	0	—	—	0	—	—
13	A	a	A	—	A	—	0	—	—	0	—	—
14	A	A	A	—	A	A	A	—	—	A	—	—
15	A	A	a	—	A	—	0	—	—	A	A‡	—
16	A	A	A	—	A	—	0	—	—	?	—	—
17	A	—	A	—	A	—	0	—	A	0	—	—
18	A	A	A	a	A	—	0	—	—	A	A	A
19	a	—	A	—	—	—	0	—	A	—	—	—
20	A	A	A	—	A	a	0	—	—	—	—	—
21	A†	A	A	—	A	0	0	Op.	0	0	0	0
Group 2												
22	A	A	A	—	A	0	0	0	—	0	0	0
23	A	A	A	A	A	A	A	A	A	—	A	—
24	A	A	A	—	A	A	A	A	—	—	—	—
25	A	A	A	—	A	—	0	—	—	—	—	—
26	A	A	A	—	A	A	0	0	A	0	A	A
27	A	a	A	—	0	—	0	0	—	0	—	0
28	A	A	A	—	—	0	0	0	0	0	0	—
29	A	A	A	?	A	—	—	—	—	—	—	—
30	A	A	A	—	a	—	0	Op.	—	—	—	—
31	A	A	A	—	A	—	0	—	A	0	—	—
32	A	A	A	—	A	—	0	—	0	0	0	0
33	A	A	A	—	a	A	0	—	—	—	A	—
34	A	A	A	a	A	0	0	A	A	a	A	A
35	A	A	A	—	A	—	0	0	—	a	—	—
36	A	A	A	—	A	A	0	A	A	0	—	A
37	A	—	A	—	?	A	0	—	0	0	0	0
38	a	—	A	—	—	0	0	0	—	0	0	0
39	A	—	A	—	—	a	0	a	—	0	a	—
40	A	A	A	a	A	—	0	Op.	a	0	a	a
41	A	A	A	A	A	A	0	Op.	A	0	A	A
42	A	A	A	—	A	—	0	—	A	0	—	—
43	A	A	A	—	a	—	0	—	—	0	0	—
44	A	A	a	—	A	a	0	—	a	0	—	—
45	A	A	A	A	A	a	0	—	—	0	—	—
46	A	A	A	—	A	A	0	Op.	—	—	—	a
47	A	A	A	—	a	A	0	—	—	—	—	—
48	A	A	A	—	A	—	0	Op.	—	0	0	—
49	A	A	A	—	A	0	0	—	a	0	—	—
50	A	A	A	—	A	—	0	—	—	0	—	—
51	A	A	A	—	A	A	0	A	A	—	A	A
52	A	—	A	—	A	—	0	—	A	—	—	—
53	A	a	A	—	A	—	0	Op.	?	A	—	—
54	a	—	a	—	—	—	0	—	—	0	0	—
55	a	—	A	—	—	?	0	0	0	0	—	—
56	a	—	a	—	—	a	0	—	—	0	—	—
57	a	—	A	—	—	A	0	—	A	0	A	—
Number examined	57	57	57	57	55	51	7	43	52	23	48	50
Number with amyloid	57	47	57	10	46	20	4	8	17	8	14	11

* A indicates amyloid found; a, small amount of amyloid; —, no amyloid; 0, tissue not examined (none saved); Op., operative removal; ?, doubtful amyloid.

† Gross examination only.

‡ Pylorus.

TABLE 10.—*Distribution of Amyloid and Other Lesions in the Kidney*

			Amount of Amyloid					Tubules		Sclerosis		
			Cortex		Medulla							
Group 1	Case	Weight of Kidney, Gm.	Glomeruli	Interstitial	Capillaries	Interstitial	Thickened Bowman's Capsule	Suppression, with Dilatation of Those Remaining	Epithelial Degeneration	Arteries	Arterioles	Infiltration
	1	234	±	−	−	+	−	−	+	−	−	−
	2	515	++	+	+	±	−	+	+	−	−	−
	3	213	+	+	++	+	−	+	−	−	−	−
	4	268	++	±	+	±	−	−	+	−	−	−
	5	242	++	±	+	+	−	−	+	−	−	+
	6	427	++	+	+	−	−	++	?	−	−	+
	7	848*	±	+	−	++	−	++	−	−	−	+
	8	309	++	±	+	++	−	−	++	−	−	−
	9	315	++++	+	++	+++	+	++	−	−	−	+
	10	271	±	±	±	−	−	−	+	−	−	−
	11	326	++	+	+	++++	−	+	+	−	−	−
	12	276	+++	±	++	+++	++++	++	+	+	+	+
	13	330	+	+	+	−	+++	++	+	++	++	+
	14	415	++++	+	+++	+	+	++	+	++	++	+
	15	286	++++	++	+++	+++	++++	+++	+	++	++	+
	16	433	++++	+	+++	++	+	++	+	++	+	+
	17	512	++	−	+	+	−	+++	++	−	−	−
	18	181	++++	++	++	−	++	++	−	−	−	+
	19	270	±	−	−	±	−	−	+	−	+	−
	20	314	+++	−	+	++	−	−	−	−	−	±
	21	369	..	..	..	..	..	..	..	..	..	..
Group 2												
	22	719	++++	+	++	+	++	+	++	−	−	+
	23	238	+++	+	++	++	−	−	−	−	−	−
	24	187	++	+++	++	++	+	++	+	+	−	−
	25	210	++	++	+	+	++	++	+	+	±	+
	26	340	+++	+	++	++	−	+	+	−	−	++
	27	795	++	+	+	++	+	+	+	−	+	+
	28	225	++	−	++	++	−	−	−	−	−	+
	29	455	+++	+	++	−	−	+	++	−	−	−
	30	200	+	−	+	+	−	+	+	−	−	+
	31	351	++	+	+	++	−	−	+	+	+	+
	32	332	+	−	+	+++	−	−	−	−	−	−
	33	253	+++	−	++	++	±	+	+	±	±	+
	34	...	+++	+	++	+	−	−	+	−	−	−
	35	370	+	±	+	−	−	++	+	−	−	−
	36	164	++	−	+	++	+	−	+	−	+	−
	37	382	++	+	+	+	−	+	+	−	−	+
	38	202	±	+	−	+	+	++	+	++	+	+
	39	345	±	−	+	−	−	±	−	−	−	++
	40	...	++++	+++	++	+++	++	++	+	+++	+++	+++
	41	280	++++	+++	++	+++	++	+++	±	++	−	−
	42	...	+	++	±	++	−	+	+	±	−	±
	43	250	++	−	+	−	−	+	+	−	−	−
	44	255	++++	++	++++	+	++	+++	+	+++	−	++
	45	221	++++	+++	+++	+++	++	+++	+	++	+	+
	46	405	+	±	++	+	−	−	−	−	−	+
	47	415	±	−	±	+	−	−	−	−	−	+
	48	266	+	+	++	+++	±	−	−	−	−	−
	49	215	++	−	−	−	±	−	−	−	−	−
	50	319	+	−	+	+	−	−	+	+	±	−
	51	328	++	+	++	±	−	±	−	−	−	+
	52	350	+	−	+	−	−	±	−	−	−	−
	53	400	+	±	+	−	−	+	−	−	−	−
	54	240	±	±	±	++	−	−	−	−	−	−
	55	281	±	−	−	−	−	−	+	−	−	−
	56	342	−	−	−	−	−	+	+	+	+	+
	57	208	±	−	±	±	−	−	−	−	−	−
	Average	410.9										

* Enormous tuberculous abscess of right kidney.

It may also be stated that a low specific gravity is usually associated with amyloid in the interstitial tissue of the renal cortex. Few patients who maintained a specific gravity of 1.016 or above showed amyloid in the interstitial tissue. Only 5 of 21 showed as much as 1 plus amyloid. However, 9 of 36 patients with a low specific gravity showed no amyloid in the interstitial tissue.

SUMMARY AND CONCLUSIONS

The clinical course in 57 cases of renal amyloidosis occurring in tuberculous patients in which amyloid deposits were demonstrated in microscopic section of renal tissue stained with methyl violet at postmortem examination is presented.

Tuberculous enteritis was the clinical complication occurring most often in association with renal amyloidosis. If only pathologically verified cases are considered, the incidence of tuberculous enteritis was approximately 60 per cent. If amyloid infiltration of the intestine is added (which includes all cases in which there was a pathologic basis for the symptoms), the incidence was 70 per cent. If cases in which the diagnosis was not verified at necropsy are added, enteritis was present in 82 per cent. Thirty-six patients (65 per cent) showed tuberculous pleuritis, pericarditis or peritonitis alone or in combination.

A suppurating focus was present in 18 patients (exclusive of patients with pulmonary cavitation).

The date of the presumptive or definite onset (or both) could be determined with reasonable accuracy in 46 cases. An outstanding clinical event or complication that might be associated with the onset of renal amyloidosis occurred in 25 cases (54 per cent). Such clinical events, complications or conditions were the onset of enteritis, pleural effusion, empyema, the development of other suppurating foci, the institution of pneumothorax and other surgical procedures.

Ten patients showed no albuminuria. The average duration of albuminuria when present was twenty-five months, the median being fifteen months. The average duration of heavy albuminuria was fifteen and eight-tenths months, the median being six months. Albuminuria preceded cylindruria in 12 cases.

Fifteen patients showed no cylindruria. The average total duration of cylindruria when present was twenty-one and one-half months, the median being twelve months. The average total duration of heavy cylindruria was nineteen and three-tenths months, the median being seven months. Cylindruria preceded albuminuria in 6 instances.

Urine with a low specific gravity was the most constant manifestation of impaired renal function. It occurred in 4 of every 5 cases. It was an early finding and, contrasted with chronic nephritis, was not associated with nitrogen retention.

Impaired concentration was a frequent finding, as shown by the Volhard test performed in 12 cases. A diminished four hour output and impaired dilution occurred with decreasing frequency. The intramuscular phenolsulfonphthalein test gave normal results in 12 of 24 cases. Only 5 of 29 patients for whom nonprotein nitrogen determinations for the blood were obtained showed a nitrogen retention of 50 mg. or more per hundred cubic centimeters.

Hypertension, according to our data, occupies an inconspicuous place in the clinical picture of renal amyloidosis. It may be incidental rather than related to cause and effect.

Arteriolosclerosis of the retinal vessels is present even less often than hypertension. Retinitis was not observed in 19 patients examined. The group examined were patients with outstanding clinical symptoms.

It is approximately correct to say that one fourth of the patients with renal amyloidosis have edema at some time during the early and middle periods of the disease, and two-thirds have terminal edema. There is no agreement between the loss of albumin via the kidney and the edema.

We have constructed a table in which the presumably causative factor, albuminuria, enlargement of the liver and spleen and the low specific gravity are each assigned a one point value with respect to the diagnosis. We believe that if this is used as a guide it will lead to the early discovery of a larger number of cases of renal amyloidosis in sanatoriums for patients with tuberculosis.

In general, the greater the number of diagnostic points, the greater the amount of amyloid present in the renal tissues.

In our cases if the old textbook triad of chronic suppuration, albuminuria and enlargement of the liver and spleen had been insisted on, the diagnostic accuracy would have been 11 per cent.

ASPIRATION FOR REMOVAL OF BIOPSY MATERIAL FROM THE LIVER

REPORT OF THIRTY-FIVE CASES

EDGAR BARON, M.D.
NEW YORK

The clinical diagnosis and prognosis of hepatic disease are frequently beset with considerable uncertainty and inaccuracy, despite the aid of numerous tests of hepatic function and recent improvements in the technic of roentgen examination. As a result, patients with hepatomegaly are often subjected needlessly to exploratory laparotomy, the liver being found to be studded with metastatic carcinoma. On one recent occasion, diagnostic aspiration of the liver was performed in a case in which hepatic suppuration was suspected (case 1). Aspiration yielded a few fragments of tissue which on histologic examination showed carcinoma. This work was subsequently extended, and forty-seven additional aspirations of tissue for biopsy were performed in thirty-four cases. It was observed that, as a procedure for patients in the wards, the diagnosis of obscure hepatic disease often could be made by this method with a reasonable degree of safety. The danger of hemorrhage, which has deterred surgeons from removing specimens for study, even at operation, may be obviated if certain precautions are observed.

Hepatic aspiration is not a new procedure. As far back as 1833 Roberts [1] and Biett [2] reported its use in the treatment of hepatic suppuration and hydatid disease. It remained the treatment of choice in these two diseases until the advent of antiseptic surgery, when it gradually fell into the discard. With advances in histologic technic, it was revived as a diagnostic aid. Bingel,[3] in 1923, reported on 100 aspirations, with 2 deaths due to hemorrhage. Olivet,[4] in 1926, reported that

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From the medical service of Dr. George Baehr, the Mount Sinai Hospital.

1. Roberts: Abscess of the Liver, with Hydatids; Operation, Lancet **1**: 189-190, 1833.

2. Biett: Hydatides du foie, avec développement considerable de cet organe; ponction explorative; incision; sortie d'une grande quantité d'acéphalocystes; guérison, Gaz. d. hôp. **7**:383, 1833.

3. Bingel, A.: Ueber der Parenchympunction der Leber, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**:210-212, 1923.

4. Olivet, J.: Die diagnostische Leberparenchympunction, Med. Klin. **22**: 1440-1443, 1926.

he had performed one hundred and forty aspirations, with 3 deaths, 2 being due to hemorrhage and 1 to peritonitis. Huard [5] reported several cases and mentioned that he had outlined an abscess cavity with iodized poppyseed oil 40 per cent.

TECHNIC

The elective site of aspiration has been subject to considerable variation. Many observers recommend the intercostal approach, either in the nipple line,[3] the anterior axilla,[6] the midportion of the axilla [7] or posteriorly.[3] However, those who have recorded cases in which death was due to hemorrhage [8] have claimed that the intercostal approach is dangerous. They concluded that a tear in the parenchyma of the liver may occur as the organ descends with inspiration, since the needle may be fixed between two ribs. In all our early cases there was hepatomegaly, and aspiration could therefore be made below the costal margin. In the absence of hepatomegaly, aspiration can be done safely to the right of the epigastrium, immediately below the costal margin and in the general direction of the lower portion of the right axilla. Aspiration was performed at first intercostally, in several cases of jaundice, without untoward effects. However, in view of the potential danger, in all subsequent cases aspiration was performed below the costal margin.

As the procedure often causes a dull pain, despite the use of local anesthesia, it has been found advisable to reenforce the anesthesia with a liberal dose of a strong hypnotic. Paraldehyde, given orally in doses of from 8 to 30 cc. about one hour prior to aspiration, has been found effective in the majority of cases.

The necessary equipment includes a 20 cc. Luer-Loc or "record" syringe and a 13 gage needle, about 9 cm. long. After the administration of a local anesthetic, the skin is punctured with a bistoury. The needle is directed upward and laterally and kept fairly superficial, thus avoiding important structures, such as large vessels or bowel, Once the parenchyma of the liver has been reached, constant suction is maintained in order to obtain a core of hepatic tissue. The specimen can be freed from blood if the contents of the syringe are poured through a double thickness of gauze. The pieces of hepatic tissue are then fixed in a solution of formaldehyde U. S. P. (diluted 1:10), and the remainder of the specimen can be removed from the syringe by rinsing the instrument with solution of formaldehyde. The tissue is then sectioned in the routine manner for histologic study.

5. Huard, P.; May, J. M., and Joyeux, B.: La ponction biopsie du foie, Ann. d'anat. path. **12**:1118-1124, 1935.

6. Sims, J. M.: Treatment of Hepatic Abscess by Aspiration, Tr. M. Soc. Virginia **3**:106-111, 1879.

7. Hammond, W. A.: Some Points in the Pathology and Treatment of Hepatic Abscesses, St. Louis M. & S. J. **35**:72-76, 1878.

8. Bingel.[3] Olivet.[4]

REPORT OF CASES

Although aspiration has been performed on patients with suppurative disease of the liver, these cases have not been included here, because it is felt that this is a recognized procedure and does not belong within the scope of the present paper.

The 8 following cases are presented in detail to illustrate the diseases in which hepatic aspiration is of greatest value. The first 2 cases are representative of the cases in which there was hepatomegaly, carcinoma being suspected clinically; the diagnosis was confirmed in both cases by hepatic aspiration. In the next 2 cases there was hepatomegaly, in 1 case due to congenital cystic disease and in the other to a large cavernous hemangioma. Histories are given of 3 cases in which there were different types of hepatogenous jaundice (catarrhal icterus, coarse nodular cirrhosis and obstructive jaundice) and of a case of proved cirrhosis of the liver.

CASE 1.—C. G., a 46 year old man, had had mastectomy in the right side (presumably for carcinoma) about five years prior to his present illness. For the past two years he had received hypertonic saline solution intravenously for angina pectoris. On entry he complained of a sensation of distress in the right upper quadrant of the abdomen associated with flatulence of four weeks' duration. Immediately prior to his entry the pain became severe, and the possibility of acute cholecystitis or of acute hepatitis following therapy with saline solution was considered. On examination the entire upper portion of the abdomen was acutely tender and rigid. The temperature varied from 102 to 104 F. The leukocyte count was 20,000 and the sedimentation rate 18 mm. in sixteen minutes. It was thought that he probably had suppurative cholecystitis, with perforation and spreading peritonitis. Operative intervention was deferred because of the patient's poor condition. After a few days the fever and leukocytosis subsided, and the pain disappeared. However, the liver had enlarged, extending about 10 cm. below the costal margin. In view of this finding, the possibility that carcinoma was compressing the hepatic vein was considered. About three days later the patient again had fever and leukocytosis, associated with copious expectoration of green, mucoid sputum and signs of consolidation of the upper lobe of the right lung. With the object of differentiating between metastatic carcinoma and hepatic suppuration, a specimen was aspirated from the liver. No pus was obtained; histologic examination of the aspirated tissue showed carcinoma. The patient died, and at postmortem examination primary carcinoma of the bronchus of the upper lobe of the right lung, with extensive metastasis to the liver, was present.

Comment.—This case served to attract our attention to the diagnostic possibilities of hepatic aspiration, particularly in the diagnosis of metastatic carcinoma of the liver.

CASE 5.—S. G., a 53 year old woman, complained of pain in the right lower portion of the chest, an increase in abdominal girth and loss of 8 pounds (3.6 Kg.) in the past three months. This was later accompanied by edema of the ankles. On examination she appeared thin and emaciated. A node the size of a cherry was felt in the left infraclavicular region. The right side of the diaphragm was high and did not move with respiration. The abdomen was distended and

doughy, and there were alternating areas of flatness and resonance, which did not shift with change in the patient's position. The liver extended about 10 cm. below the costal margin. There were numerous tortuous veins extending from the inguinal region over the abdomen and chest. The current of blood was from below upward, suggesting obstruction of the inferior vena cava. The leukocyte count was 13,900 and the hemoglobin value 58 per cent. Roentgen examination of the chest showed that the right side of the diaphragm was high. A pyelogram, made after intravenous injection of a contrast medium, was unsatisfactory. The node in the left infraclavicular region was excised and showed the presence of neurofibroma. It was felt that hepatic aspiration afforded the best method of arriving at a diagnosis. A large quantity of caseous material was aspirated; this proved to be a specimen of malignant Grawitz tumor.

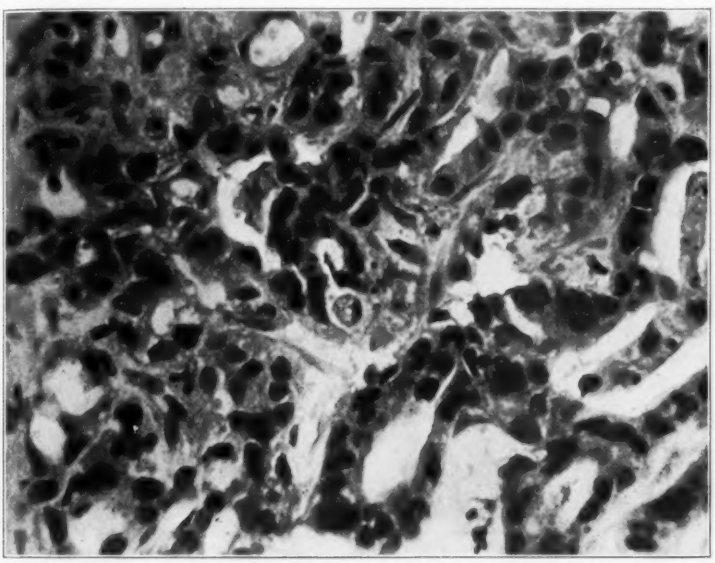

Fig. 1 (case 3).—Adenocarcinoma.

Comment.—The reason for the collateral circulation now became clear. Apparently the tumor had invaded and obstructed the inferior vena cava. The loculated abdominal fluid was attributed to peritoneal invasion.

Case 12.—B. E., a 53 year old man, had one episode of hematuria, nine years prior to admission to the hospital, which persisted for five days. He then showed progressive dyspnea on exertion. A mass developed in the upper portion of the abdomen and gradually increased in size during the past four years. On examination he appeared thin and chronically ill. The liver extended about 20 cm. below the costal margin; the surface was firm and nodular, without tenderness. The spleen and the left kidney could be palpated. There was moderate edema of the ankles. The hemoglobin value was 90 per cent, the leukocyte count 17,000 and the sedimentation rate normal. The galactose tolerance test showed values within

normal limits. Examination of stools showed no blood, ova or parasites. A congo red test showed 28 per cent retention of dye in the tissues. The value for total protein was reduced to 5.2 per cent (albumin, 3.1 per cent; globulin, 2.1 per cent). The value for urea nitrogen was 21 mg. per hundred cubic centimeters of blood. The icteric index was 1. The cholesterol content was 200 mg. and the cholesterol ester content 65 mg. per hundred cubic centimeters. Several specimens of urine revealed a trace of albumin, occasional erythrocytes and clumped leukocytes. A Rehfuss test meal showed a diminution in the content of free hydrochloric acid. Roentgen examination of the chest, long bones and gastrointestinal tract revealed no abnormality. Pneumoperitoneum showed the liver to be large, nodular and adherent to the under surface of the diaphragm. The spleen was enlarged. The reason for the hepatosplenomegaly was obscure. Cardiac failure, amyloid disease or cirrhosis seemed unlikely. In spite of the prolonged history, the possibility of carcinoma was strongly suspected by some observers. Aspiration of a specimen from the liver was carried out at two different sites, and two different types of clear fluid were obtained, one yellow and the other colorless. This limited the possible diagnoses to either echinococcosis or congenital cystic disease. The fluid contained no scolices; the complement fixation test for echinococcosis gave negative results for both fluid and blood. A pyelogram showed the presence of congenital cystic disease of the kidneys.

Comment.—In this case hepatic aspiration provided the first clue to the correct diagnosis, as the presence of congenital cystic disease of the liver and kidneys had not been suspected.

Case 15.—P. S., a 41 year old woman, since pregnancy seven years ago, had complained of severe epigastric pain which occurred one or two hours after meals and was relieved by self-induced vomiting or with sodium bicarbonate. She attributed a loss of 52 pounds (23.6 Kg.) to the fact that she was afraid to eat. Ten months prior to entry her appendix was removed in an effort to alleviate the pain. At that time a small cutaneous cavernous hemangioma was removed from the left temporal region.

On examination the patient appeared thin and emaciated. The left lobe of the liver extended about 10 cm. below the costal margin; its surface was smooth and acutely tender. The right lobe was barely palpable. There were no significant laboratory findings. Roentgen examination of the chest and abdomen and a pyelogram shed no light on the diagnosis. Pneumoperitoneum showed a mass, the size of a grapefruit, merging with the shadow of the liver. Examination of the gastrointestinal tract showed that the stomach was pushed to the left, the lesser curvature being compressed by an extrinsic mass. The second portion of the duodenum was drawn toward the liver and fixed. As all the diagnostic measures had failed to reveal the nature of the underlying disease, an attempt was made to aspirate material for biopsy. The skin was anesthetized, but each time that an attempt was made to anesthetize the peritoneum, venous blood was aspirated. Since the surface of the liver does not ordinarily contain large blood vessels, it was concluded that the hepatic enlargement could be explained by the presence of a large cavernous hemangioma. The surmise was confirmed at operation, the hemangioma being merged with the left lobe of the liver. As there was no line of cleavage, resection was impossible.

Comment.—Fortunately hepatic aspiration was not completed in this case, for the attempt to introduce a large needle into a hemangioma might possibly have resulted disastrously.

CASE 19.—G. R., a 37 year old man, a Puerto Rican who had resided in the United States for thirty years, complained that two weeks prior to admission to the hospital he experienced nausea, vomiting and anorexia. One week later he had a dull epigastric pain, accompanied by jaundice, dark urine and clay-colored stools. There was no history of ingestion of drugs. On examination he appeared deeply jaundiced. The liver and spleen were both palpable. The stool was brown and showed a strongly positive reaction for urobilinogen. The urine showed a 3 plus reaction for bile and urobilinogen in a dilution of 1 to 20. The cholesterol content was 230 mg. and the cholesterol ester content 96 mg. per hundred cubic centimeters of blood. The icteric index was 38 (acetone extraction method). The bilirubin value was 10 mg. per hundred cubic centimeters. The van den Bergh test showed a prompt positive reaction. The Wassermann reaction was

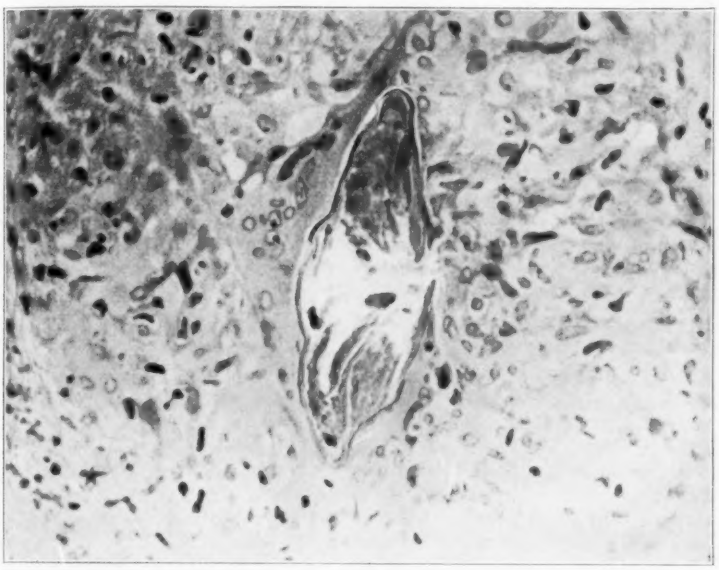

Fig. 2 (case 19).—Tubercle-like reaction surrounding an ovum of Schistosomum.

negative. A galactose tolerance test showed impaired hepatic function (9.49 Gm. was excreted). A sodium benzoate test showed an excretion of less than 0.96 Gm.

The data indicated that this was probably a case of typical catarrhal jaundice in an early stage. It was felt that aspiration of biopsy material would be of value in determining the underlying pathologic condition and would also serve as a means of comparison with tissue obtained from patients with other types of jaundice. The specimens showed parenchymatous degeneration and inspissated bile in the bile capillaries. Aspiration was repeated several weeks later, after subsidence of the icterus. On this occasion there was no evidence of degeneration or icterus, although the icteric index had not yet returned to normal. Incidentally, a granuloma was discovered surrounding an ovum of Schistosomum mansoni. Examination of the stool subsequently revealed several ova. It seemed probable that the parasite had remained viable for at least thirty years.

CASE 23.—L. H., a 48 year old woman, eight weeks prior to admission to the hospital began to complain of anorexia, nausea and malaise. Several days later there appeared jaundice, which rapidly became intense. Although the stools were light at the onset, they soon resumed their normal color. Six weeks after the onset she experienced moderate pruritus. No history of biliary colic was elicited. On examination she appeared deeply icteric. The liver extended 10 cm. below the costal margin. Throughout the period of observation specimens of urine contained abundant quantities of bile. Urobilinogen was present in dilutions varying from 1:5 to 1:160. The cholesterol content of the blood was 460 mg. and the cholesterol ester content 110 mg. per hundred cubic centimeters. The icteric index varied from 10 to 40 units. The bilirubin value was 3.5 mg. The van den Bergh test showed a prompt positive reaction. Culture of bile obtained by duodenal drainage revealed a bacillus of the diphtheroid group, Streptococcus haemolyticus (beta), Staphylococcus albus and Bacillus welchii. The gallbladder was not visualized by means of the Graham test, and no opaque stones were seen. The galactose test revealed an excretion of 8.11 Gm. The sodium benzoate test showed an excretion of less than 1.2 Gm.

In view of the long history of unremittent jaundice, exploratory operation seemed indicated. However, the hepatic function tests suggested severe primary degeneration of the liver. After eleven weeks of jaundice, hepatic aspiration was performed, the biopsy specimen showing chronic and acute interstitial hepatitis, parenchymatous degeneration and icterus. No inspissated bile was present in the bile capillaries. In view of these findings it appeared that the jaundice could be attributed either to coarse nodular cirrhosis following severe degeneration of the liver or cholangitis lenta. When seen five months after the onset, the patient was still icteric, with no signs of recovery.

CASE 25.—R. S., a 65 year old woman, had lost considerable weight during the past six months. She had complained of jaundice, pruritus, dark urine and tendency to bruise easily for four weeks prior to admission to the hospital. On examination she was moderately icteric. The liver extended about 10 cm. below the costal margin; the edge was hard and irregular. The urine showed a 4 plus reaction for bile and urobilinogen in a dilution of 1 to 5. The sedimentation rate was 18 mm. in seventeen minutes; the leukocyte count was 20,000. A specimen of stool contained a trace of urobilinogen. The cholesterol content of the blood was 340 mg. per hundred cubic centimeters. The icteric index was 30. The value for bilirubin was 5 mg. per hundred cubic centimeters. The van den Bergh test showed a prompt positive reaction. The galactose tolerance test gave values within normal limits, although the sodium benzoate test revealed an excretion of only 0.4 Gm. The clinical diagnosis in this case was obstructive jaundice, possibly due to carcinoma of the head of the pancreas. The hepatic aspiration, which showed inspissated bile in the bile capillaries and acute inflammation of the periportal fields, confirmed the impression of obstructive icterus. The patient refused cholecystogastrostomy as a palliative procedure.

CASE 32.—J. Y., a 52 year old woman, had had mild recurrent attacks of pain in the upper abdominal region during the past two years. The pain had become more severe during the past three months and was associated with a dragging sensation in the left upper quadrant. The liver extended 8 cm. below the costal margin and felt firm. The spleen extended 10 cm. below the costal margin. The leukocyte count was 1,800, with a normal differential count. The number of platelets was reduced to 90,000. The cholesterol content of the blood was 265 mg. and the cholesterol ester content 30 mg. per hundred cubic centimeters. The

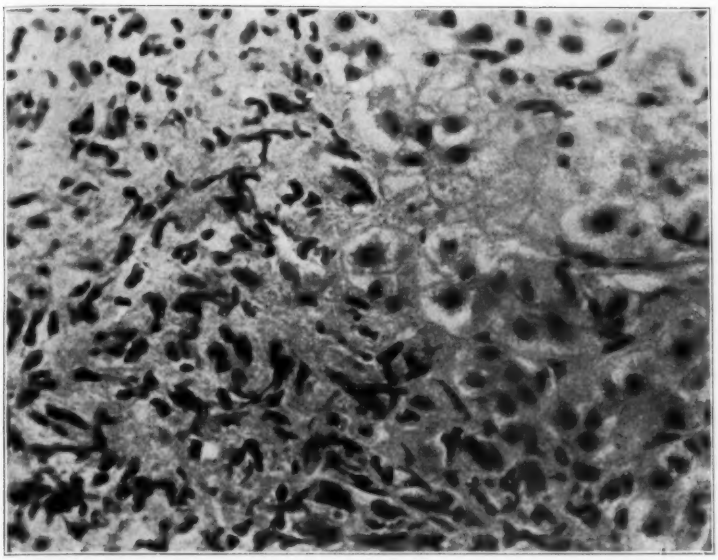

Fig. 3 (case 23).—Hepatic degeneration with fibrosis.

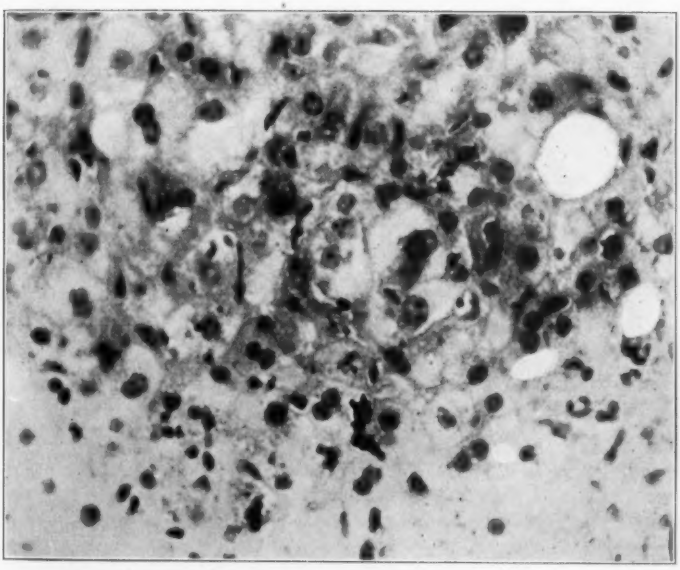

Fig. 4 (case 25).—Thrombi in bile capillaries.

Takata-Ara test of the blood serum gave a 2 plus reaction. Pneumoperitoneum showed hepatosplenomegaly. Sternal and splenic punctures revealed no abnormal findings. It was felt that the probable diagnosis was Laënnec's cirrhosis, possibly with thrombosis of the splenic vein. Although the biopsy specimen obtained by hepatic aspiration showed an increase in fibrous tissue, this was not sufficiently characteristic to warrant the diagnosis of cirrhosis. Since the patient's symptoms appeared to be due to enlargement of the spleen, splenectomy was performed. The spleen was large and succulent and contained about 500 cc. of blood. The liver presented the appearance typical in cases of Laënnec's cirrhosis. The patient made an uneventful recovery. The platelet count rose to 750,000 and the leukocyte count to 8,800.

Comment.—The data relative to the cases in which hepatic aspiration was performed are presented in the accompanying table, with the clinical impression prior to aspiration, the histologic details and the ultimate course.

COMPLICATIONS

While no serious complications were encountered in the group of cases reported in this paper, other observers have reported several types of untoward accidents. These may be classified under the following headings:

1. Hemorrhage
2. Infection
   - (*a*) Introduced from the outside
   - (*b*) After perforation of a hollow viscus
   - (*c*) After entrance into an abscess cavity

Hemorrhage is the most common cause of death, according to the reports in the literature. Five instances in all have been reported, by Bingel,[3] Olivet [4] and Toullec;[9] these occurred in cases in which aspiration was probably performed intercostally. The bleeding in these instances was attributed to the fact that the needle was held between two ribs, the liver being torn as it descended with inspiration. This complication can be eliminated by performing the aspiration below the costal margin, and the large vessels can be avoided if the needle is kept superficial.

When postmortem examination was performed in the cases reported in the present study, there was no evidence that bleeding had occurred. Usually the site of aspiration could not be identified, or was revealed by a minute area of organized thrombus. Minor bleeding probably does occur in some cases, as is shown by the fact that vomiting may take place immediately after the needle is withdrawn. A patient who is awake may complain of pain at the site and also of pain referred to the region of the right shoulder. Sometimes there is a slight rise in temperature,

9. Toullec, F., and Huard, P.: La ponction exploratrice du foie, Monde méd., Paris **45**:990-999, 1935.

Data Regarding Thirty-Five Cases

Case No.	Initials	Diagnosis	Pathologic Report on Tissue Aspirated	Comment
Carcinoma				
1	C. G.	Metastatic carcinoma or hepatic abscess	Carcinoma	Postmortem diagnosis: primary carcinoma of bronchus of upper lobe of right lung, with hepatic metastases
2	F. H.	Metastatic carcinoma	Carcinoma	No operation
3	J. K.	Metastatic carcinoma	Adenocarcinoma	No operation
4	F. F.	Metastatic carcinoma	Anaplastic carcinoma	Postmortem diagnosis: primary gastric carcinoma with hepatic metastases
5	S. G.	Metastatic carcinoma	Malignant Grawitz tumor	No operation
6	M. T.	Metastatic carcinoma; cirrhosis	1. Malignant growth; possibly sarcoma 2. Normal liver 3. Normal liver; colonic mucosa aspirated	Exploratory laparotomy was performed three days after last aspiration; no leak or peritoneal reaction; postmortem examination showed primary gastric carcinoma with hepatic metastases
7	L. H.	Metastatic carcinoma	Adenocarcinoma	No operation
8	S. G.	Metastatic carcinoma	1. Few tumor cells suggestive of carcinoma 2. Carcinoma 3. Carcinoma	No operation
9	L. B.	Metastatic carcinoma	1. No hepatic tissue 2. Lymphocytic focal infiltration; inflamed granulation tissue 3. Densely arranged spindle cells with occasional mitotic figures	Postmortem diagnosis: primary bronchogenic carcinoma with hepatic metastases
10	E. T.	Metastatic carcinoma	Immature cell carcinoma (small cell type)	No operation
11	D. M.	Cirrhosis with ascites	Scirrhous carcinoma	No operation
12	B. E.	Metastatic carcinoma	No tissue was obtained; only clear, yellow fluid	Congenital cystic disease of liver and kidneys
13	H. R.	Metastatic carcinoma or abscess	Normal liver	No operation; subsequent course slowly downhill; carcinoma probably present and not found
14	J. R.	Carcinoma of lung; ascites	Normal liver	Metastases probably present
15	P. S.	Metastatic carcinoma	Blood only	Cavernous hemangioma present at operation
16	M. L.	Metastatic carcinoma	Fatty liver	Resection of carcinoma of colon 10 years ago; probably no metastases
17	G. K.	Carcinoma of the stomach	Normal liver	At operation, primary gastric carcinoma; liver, free from metastases
18	E. K.	Hepatomegaly; amyloid disease or cirrhosis	1. Normal liver 2. Carcinoma	Diagnosis of carcinoma not suspected clinically until appearance of ascites
Jaundice				
19	G. R.	Catarrhal jaundice	1. Hepatic degeneration and icterus 2. Schistosomiasis	Probably two independent diseases, namely, catarrhal icterus and schistosomiasis; ova subsequently recovered in stool
20	M. E.	Jaundice; multiple parasitic infestation	Normal liver	S. mansoni, Necatur americanus and Trichiuris recovered from stool
21	O. B.	Catarrhal jaundice	Normal liver	Specimen removed at fourth week, when jaundice was receding
22	D. S.	Catarrhal jaundice	Slight periportal inflammation; no hepatic degeneration	Specimen taken late in disease; uneventful recovery

Data Regarding Thirty-Five Cases—Continued

Case No.	Initials	Diagnosis	Pathologic Report on Tissue Aspirated	Comment
Jaundice—Continued				
23	L. H.	Coarse nodular cirrhosis	1. Hepatic degeneration 2. Thickening of periportal fields and infiltration with polymorphonuclear leukocytes and lymphocytes	After five months, jaundice still present
24	J. R.	Coarse nodular cirrhosis	1. Fibrosis and infiltration with leukocytes 2. Bile casts	Jaundice persisted after five months
25	R. S.	Carcinoma of pancreas	Inspissated bile in bile capillaries	No operation
26	J. E.	Carcinoma of pancreas	Obstructive icterus and acute cholangiolitis	No operation
27	K. H.	Carcinoma of pancreas	Obstructive jaundice with cholangiolitis	At operation: primary papillary adenocarcinoma of gallbladder; obstruction due to glandular metastases
28	L. S.	Hepatitis or carcinoma of pancreas	Obstructive jaundice; subacute cholangiolitis	Jaundice slowly receding; diagnosis not clear
29	J. B.	Carcinoma of pancreas	Chronic and acute periportal inflammation; obstructive icterus	At operation: carcinoma of head of pancreas, with hepatic metastases
30	I. N.	Anemia; hepatomegaly; jaundice	1. Hemosiderosis and inflammation 2. Hemosiderosis and inspissated bile in bile capillaries 3. Hemosiderosis and periportal round cell infiltration	Aplastic anemia confirmed by bone marrow examination; jaundice appeared after transfusion; liver became progressively larger; cause still obscure
Miscellaneous				
31	I. W.	Cirrhosis	Normal liver	No operation; clinical diagnosis clearly indicative of cirrhosis
32	J. Y.	Cirrhosis	Normal liver	At operation: Laënnec's cirrhosis with splenomegaly
33	N. P.	Cirrhosis	Periportal inflammation; no cirrhosis	No operation; final clinical diagnosis, cirrhosis
34	Y. S.	Cholecystitis	Normal liver	At operation: stone in common bile duct without obstruction
35	D. N.	Diabetes mellitus	Normal liver	Hepatomegaly probably due to ptosis

which persists for forty-eight hours. These symptoms may be due to extravasation of blood in the peritoneal cavity. The vomiting and the pain in the shoulder, first noted by Dieulafoy,[10] in 1872, can be attributed to the presence of a small amount of blood on the under surface of the diaphragm, but otherwise these symptoms appear to be of little importance.

Local infection at the site of the puncture or peritonitis introduced from without can be attributed only to improper technic.

Olivet [4] reported a death due to peritonitis, which may have followed perforation of the bowel, resulting in an intestinal leak. In 1 of our first cases (case 6) a small piece of colonic mucosa was recovered, but there was no untoward reaction. When the patient was operated on, three days later, neither the site of aspiration in the liver nor the

10. Dieulafoy, G.: Kystes hydatiques, Gaz. d. hôp. **45**:586, 595, 603, 614, 621, 644, 691 and 780, 1872.

site of entry into the colon could be found. There was no intestinal leak or peritoneal reaction. The possibility of peritonitis after aspiration of a hydatid cyst or a hepatic abscess is remote; indeed, this was the method of choice for the treatment of these two conditions during the past century, and many authors stressed the point that peritonitis was not one of the complications encountered.

COMMENT

The cases in which hepatic aspiration was performed can be grouped according to the diagnostic problems presented:

1. Hepatomegaly without jaundice (18 cases)
   - (*a*) Carcinoma proved (12 cases)
   - (*b*) Carcinoma probably missed (2 cases)
   - (*c*) Carcinoma probably not present (2 cases)
   - (*d*) Other diseases proved (2 cases)
     - Congenital cystic disease
     - Cavernous hemangioma
2. Jaundice (12 cases)
   - (*a*) Catarrhal icterus (4 cases)
   - (*b*) Coarse nodular cirrhosis (2 cases)
   - (*c*) Obstructive jaundice (5 cases)
   - (*d*) Unclassified (1 case)
3. Cirrhosis of the liver (3 cases)
4. Miscellaneous (2 cases)

There are many patients with hepatomegaly who are suspected of having metastatic carcinoma but in whom the primary site cannot be established by the usual methods. In the past these patients have been routinely subjected to unnecessary exploration. In the majority of instances the diagnosis of carcinoma can be established definitely by hepatic aspiration, thus eliminating the attendant operative risk. Conversely, the finding of conditions other than a malignant growth will render the prognosis more favorable.

In cases in which carcinoma is suspected it has been found that occasionally as many as three aspirations are necessary before the diagnosis can be substantiated, since small metastases may easily be missed by the aspirating needle.

Four patients with catarrhal jaundice had hepatic aspiration performed. Only 1 of these showed definite pathologic changes by the routine methods of staining. In this instance the procedure was performed on the ninth day of jaundice. In the other cases aspiration was performed three to six weeks after the onset of jaundice and showed no definite abnormalities. Although the group is far too small to permit the drawing of any conclusions concerning the pathologic picture

of catarrhal jaundice, there is suggestive evidence that the parenchymal changes do not persist for more than a few weeks, even though the icteric index remains elevated.

The patients for whom a diagnosis of coarse nodular cirrhosis was made had been icteric for four or five months. The hepatic function tests showed considerable hepatic damage. The specimens obtained by hepatic aspiration showed parenchymal degeneration, thickening, fibrosis and acute and chronic inflammation of the periportal fields. Occasionally inspissated bile was seen in the bile capillaries.

In the 5 cases of obstructive jaundice there were inspissated bile in the bile capillaries and acute and chronic cholangiolitis. There was no fibrosis or degeneration of the parenchyma of the liver. In all the cases, carcinoma of the head of the pancreas was suspected. At operation in 1 case, primary carcinoma of the gallbladder was present, the obstruction of the common bile duct being caused by a metastatic lymph node.

There was 1 case of unexplained anemia, in a 78 year old man with hepatomegaly. On one occasion, after a transfusion reaction, he became icteric for about two weeks. The jaundice was not hemolytic, and the anemia was shown to be aplastic by bone marrow examination. Hepatic aspiration on three occasions showed hemosiderosis and occasionally inspissated bile in the bile capillaries. The case still constitutes a diagnostic problem.

It has been observed that the specimens of hepatic tissue obtained by aspiration in cases of cirrhosis do not show sufficient structural detail to warrant the diagnosis of cirrhosis. Apparently the parenchymal tissue is aspirated easily enough, but the tough, fibrous tissue stroma is largely left behind. However, the procedure is still indicated in what may appear to be a case of typical cirrhosis, as the signs and symptoms may be confused with those of carcinoma.

In the study of hepatic disease, laboratory procedures can only reflect the alterations in function produced by the primary disturbance and are open to error in interpretation. Hepatic aspiration, on the other hand, may yield direct information about the pathologic changes in the liver. It offers a safe, rapid, inexpensive and reliable method of reaching the correct diagnosis and in some cases the only means of studying the pathologic changes associated with certain hepatic diseases. By its use many patients have been spared the ordeal of a useless laparotomy.

SUMMARY

Forty-eight hepatic aspirations have been performed on 35 patients. There have been no serious complications after the employment of this procedure.

The subcostal approach is preferred to the intercostal route, in order to obviate the danger of hemorrhage.

In 1 case a small piece of colonic mucosa was recovered, owing to penetration of the colon. There were no untoward results.

Hepatic aspiration has been of great value in the diagnosis of metastatic carcinoma and in the differential diagnosis of jaundice. It is also of value in the diagnosis of less common diseases, such as congenital cystic disease, cavernous hemangioma and schistosomiasis. It has been found of little value in the diagnosis of cirrhosis.

NOTE.—Since this paper was submitted for publication there has been 1 death directly attributable to the procedure. The case was that of a man with extensive metastatic carcinoma of the liver. Death was due to a small rent in the surface, measuring about 1 cm. This resulted in an exsanguinating hemorrhage.

RELATION OF CARDIAC OUTPUT TO CONGESTIVE HEART FAILURE

JOHNSON McGUIRE, M.D.

ROSE SHORE, B.A.

VIRGIL HAUENSTEIN, M.D.
AND
FRED GOLDMAN, M.D.
CINCINNATI

Few studies relating to cardiac output in the presence of congestive failure have been made by acceptable technical methods. Lauter,[1] employing the direct Fick method in 3 cases of cardiac decompensation, found markedly subnormal values for the cardiac output and especially for the output per beat. Employing a similar technic, McGuire, Hauenstein and Shore [2] studied 5 cases of organic heart disease. Of these cases, decompensation was severe in 1, mild in 2 and slight in 1. In the case of severe failure the cardiac output was normal, a finding we have rarely encountered in patients subsequently studied by the acetylene method.

Harrison [3] investigated the cardiac output with the three sample acetylene method in 19 cases of congestive failure. He concluded:

> Persons with congestive heart failure may, and often do, have diminished circulatory minute volume. There is *no* correlation between the clinical state on the one hand and either the output of the heart per minute or the arteriovenous oxygen difference on the other.

Kinsman, Moore and Hamilton,[4] employing their dye injection method, found that the majority of patients with cardiac failure had a

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From the Department of Internal Medicine, University of Cincinnati, and the Cardiac Laboratory, Cincinnati General Hospital.

1. Lauter, S.: Kreislaufprobleme, München. med. Wchnschr. **77**:526, 1930.

2. McGuire, J.; Hauenstein, V., and Shore, R.: Cardiac Output in Heart Disease Determined by the Direct Fick Method, Including Comparative Determinations by the Acetylene Method, Arch. Int. Med. **60**:1034 (Dec.) 1937.

3. Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1936, p. 64.

4. Kinsman, M.; Moore, J. W., and Hamilton, W. F.: Studies on the Circulation: Analysis of Some Problems of the Circulation in Man in the Normal and in Pathological States by the Use of the Injection Method, Kentucky M. J. **31**:285, 1933; personal communication to the authors.

decreased cardiac output. Starr and his co-workers,[5] employing their modification of the ethyl iodide method, reported decreased cardiac output for patients who had recovered from cardiac failure, as did Altschule and Volk,[6] who used the acetylene method.

Thus it is evident that no uniformity of opinion exists regarding the relation of cardiac output to congestive heart failure. It was the purpose of this study to determine if any correlation exists between the cardiac output and the degree of failure, as evidenced by the clinical picture and as measured by vital capacity, velocity of the flow of blood and level of venous pressure. Twenty patients with varying degrees of congestive heart failure were studied in this series. Repeated studies of certain of these patients who regained compensation will be reported later.

METHOD

The vital capacity was measured by the standard established by Blumgart and Weiss.[7] The circulation time from arm to carotid sinus was studied in the majority of patients by the cyanide method of Robb and Weiss.[8] Whenever decholin or saccharine was employed this is indicated in the tables. Venous pressure in the cubital vein was determined by the direct method of Moritz and Tabora.[9] Fluoroscopic examination of the heart was made in all cases, with especial reference to the amplitude of excursion of the cardiac borders.

The acetylene method of Grollman,[10] as modified by Grollman, Friedman, Clark and Harrison[11] for use in the presence of pulmonary congestion, was employed

5. Starr, I.; Donal, J. S.; Margolies, A.; Shaw, R.; Collins, L. H., and Gamble, C. J.: Studies of the Heart and Circulation in Disease: Estimations of Basal Cardiac Output, Metabolism, Heart Size and Blood Pressure in Two Hundred and Thirty-Five Subjects, J. Clin. Investigation **13**:561, 1934.

6. Altschule, M. D., and Volk, M. C.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Failure and Angina Pectoris: XVIII. The Cardiac Output Following Total Thyroidectomy in Patients With and Without Congestive Heart Failure, with a Comparison of Results Obtained with the Acetylene and Ethyl Iodide Methods, Arch. Int. Med. **58**:32 (July) 1936.

7. Blumgart, H. L., and Weiss, S.: Clinical Studies on the Velocity of Blood Flow: X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, J. Clin. Investigation **5**:379, 1928.

8. Robb, G. P., and Weiss, S.: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, Am. Heart J. **8**:650, 1933.

9. Moritz, F., and Tabora, D. V.: Ueber ein Methode beim Menschen den Druck in oberflächlichen Venen exact zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

10. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

11. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**:751, 1933.

for the determination of the cardiac output in all cases. Oxygen consumption was determined in all cases with the Benedict-Roth metabolism apparatus.

The fundamental principles underlying the acetylene method were described by Grollman as follows:

"If one inspires a mixture containing a foreign gas (i. e., a gas not normally present in the body) this gas will enter the blood stream and be carried to the tissues. If the gas possesses certain physical properties, as regards its solubility and diffusibility, it will distribute itself between the alveolar air and the blood in accord with the physical laws of the solution of gases in liquids. According to this law the volume of the gas dissolving in the liquid will be proportional to its tension above the liquid. A knowledge of the solubility of the gas in the liquid allows us to calculate the amount which will dissolve per unit volume of liquid when the gas is at any given tension. Conversely by measuring the amount of gas dissolved in the liquid and its tension above the liquid, we can calculate the amount of liquid which has been brought into equilibrium with the gas. This is the fundamental idea underlying the determination of the cardiac output by the foreign gas principle. The blood flowing through the lungs enters into equilibrium with a foreign gas. The tension and rate of absorption of this gas are determined, from which in turn is calculated the volume of blood flowing through the lungs in unit time. Since, except in certain rare congenital anomalies, all the blood pumped by the heart passes through the lungs, we are thus determining the cardiac output."

The patients selected for study had entered the hospital because of the symptoms associated with congestive heart failure. No patients with such complicating factors as anemia, advanced emphysema or fever, as determined by mouth, were examined. Owing to the fact that the procedure associated with this method for measuring cardiac output requires the cooperation of the subject, we were unable to study patients with cardiac asthma or with dyspnea severe enough to prevent cooperation. However, as soon as the decrease in dyspnea made the rebreathing procedure possible, the subjects were trained, and the cardiac output was determined on the following morning. The vital capacity, venous pressure and circulation time were measured the same morning. All determinations were made under basal conditions. The patients without exception were receiving digitalis at the time the studies were made. The majority of investigators have expressed the belief that digitalis increases or has no constant influence on the output of the dilated heart with regular rhythm.[12]

Two values for the arteriovenous oxygen differences were obtained in each case from analyses of the three samples collected during rebreathing. Inadequate mixture in the lung-bag system resulting from pulmonary congestion and errors due to recirculation were minimized by discarding all determinations when the arteriovenous oxygen differences between samples 1 and 2 and 2 and 3 differed

12. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: II. The Effect on the Output of Hearts in Heart Failure with Congestion in Human Beings, J. Clin. Investigation **11**:917, 1932. Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1936. Starr, I.; Gamble, C. J.; Margolies, A.; Donal, J. S.; Joseph, N., and Eagle, E.: A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size; on Respiration, on Metabolic Rate and on the Electrocardiogram, J. Clin. Investigation **16**:799, 1937.

by more than 10 per cent, save for 2 patients (cases 10 and 14), whose differences were 12.5 per cent and 1 patient (case 19) for whom the arteriovenous oxygen difference between samples was 15 per cent.

In evaluating the severity of failure three physicians classified the patients as showing 1 plus, 2 plus, 3 plus and 4 plus degrees of failure on the basis of the clinical findings. These physicians were not familiar with the results of the measurements of cardiac output and were consequently unprejudiced in their effort to classify appropriately the condition of each patient. Nine of the patients studied in this series died. Nine are living, 5 of whom are cardiac invalids and 4 are able to work. The 2 remaining patients cannot be traced.

TABLE 1.—*Determinations of Cardiac Output for Sixteen Normal Subjects*

Patient	Arterial Blood Pressure, Mm. Hg	Vital Capacity, Percentage of Normal	Basal Metabolic Rate	Arteriovenous Oxygen Difference, Cc. per Liter	Cardiac Output: Liters per Square Meter	Cardiac Output: Cc. per Beat	Comment
1	130/ 80	53	— 3	46.4	2.59	56	Rheumatoid arthritis
2	120/ 80	100	—10	67.5	1.84	39	Normal
3	.....	97	—10	64.8	1.93	40	Normal
4	.....	70	+12	59.2	2.39	47	Normal
5	140/ 80	97	— 6	65.2	1.96	49	Convalescent from phenobarbital poisoning
6	108/ 70	107	— 9	59.2	2 14	75	Hemophilia
7	100/ 70	113	— 4	65.8	2.02	51	Normal
8	140/110	97	— 3	57.9	2.32	51	Convalescent from hernioplasty
9	110/ 80	93	— 1	76.2	1.80	36	Normal
10	110/ 74	100	—15	62.5	1.90	40	Convalescent from varicocelectomy
11	100/ 70	89	— 6	58.5	2.18	63	Convalescent from hernioplasty
12	140/100	90	— 3	56.0	2.21	50	Peripheral neuritis with foot drop
13	120/ 80	85	— 5	73.3	1.70	44	Convalescent from hernioplasty
14	98/ 78	96	—12	62.3	1.96	50	Normal
15	110/ 70	73	— 1	52.5	2.35	42	Neurocirculatory asthenia
16	120/ 90	111	+15	68.2	2.33	52	Normal
Average.....				62.2	2.10	49	

RESULTS

Comparative studies with the acetylene and the direct Fick method have shown close parallelism of results in cases of decompensation under basal conditions, although the absolute values were lower with the acetylene method.[2]

We believe, therefore, that the results to be described are significant, but realize that probably no indirect method of measuring cardiac output is accurate to the cubic centimeter.

Table 1 summarizes the data concerning 16 normal subjects. The mean value for cardiac output in this group was 2.16 ± 0.03 liters per square meter of body surface per minute. The coefficient of variability was 10 per cent.

Table 2 summarizes the data concerning 20 patients with congestive heart failure. The mean value for cardiac output in this group was

TABLE 2.—*Circulatory Studies of Twenty Patients with Congestive Heart Failure*

Patient	Age	Diagnosis	Arterial Blood Pressure, Mm. Hg	Clinical Degree of Failure	Dyspnea	Edema	Vital Capacity, Percentage of Normal	Circulation Time, Sec.*	Venous Pressure, Cm. of Water	Basal Metabolic Rate, Percentage of Normal†	Arteriovenous Oxygen Difference, Cc. per Liter‡	Cardiac Output, Liters per Square Meter†	Cardiac Output per Beat, Cc.
1	46	Syphilitic aortitis with aortic insufficiency	150/ 68	+	++	+	53	39	9.0	+10	92.6 96.5	1.53	34.0
2	61	Arteriosclerotic and hypertensive heart disease	150/100	++++	+++	++++	23 ?	..	....	— 9	119.0 110.0	0.91?	13.5
3	49	Arteriosclerotic heart disease with hypertension	180/140	+++	+++	+	42	23	10.6	+20	94.5 100.0	1.62	32.0
4	50	Arteriosclerotic and hypertensive heart disease	160/130	+++	+++	++	40	40 (D)	14.0	+ 8	116.0 107.0	1.24	19.0
5	36	Rheumatic heart disease; mitral stenosis; auricular fibrillation	130/ 85	++	++	+	37	38 (D)	15.0	+13	120.0 127.0	1.35	24.0
6	75	Arteriosclerotic and hypertensive heart disease; pulmonary emphysema	140/100	++++	++++	++++	35	..	16.0	+34 ?	95.5 93.5	1.58 ?	29.0
7	49	Aortic insufficiency; syphilitic aortitis	210/ 10	++	++	++	35	..	....	+42	79.7 83.5	2.27	40.0
8	27	Cardiac dilatation and hypertrophy; tuberculous pericarditis without constriction (autopsy)	110/ 74	+++	+	++++	40	..	....	+20	128.0 140.0	1.11	17.0
9	38	Rheumatic heart disease; mitral stenosis; aortic insufficiency	110/ 68	+	0	+	68	25 (D)	4.0	+20	79.0 80.3	2.04	49.0
10	47	Arteriosclerotic and hypertensive heart disease	160/120	++	++	0	42	32 (D)	9.0	+23	120.0 105.0	1.43	36.0
11	52	Syphilitic aortitis	120/ 80	+++	+	++++	29 ?	43 (S)	18.0	—19 ?	148.0 135.0	0.73 ?	12.4
12	56	Hypertensive and coronary heart disease	130/115	+	+	0	55	..	....	— 6	59.0 53.7	2.09	40.0
13	41	Syphilitic and hypertensive heart disease; aortic insufficiency	170/ 70	+++	++	++	63	30	5.0	+19	87.0 85.0	1.82	39.0
14	44	Coronary heart disease; hypertension	140/115	++	++	+	73	20	6.3	+14	91.0 104.0	1.40	23.0
15	39	Syphilitic heart disease; aortic insufficiency	150/ 40	++++	+++	+++	33	43	14.5	+14	136.0 137.0	1.13	16.3
16	47	Arteriosclerotic and hypertensive heart disease	130/110	++++	+++	+++	48	31 (D)	13.0	+20	134.5 125.2	1.20 ?	22.0
17	49	Syphilitic aortitis; aortic insufficiency	140/ 36	++	++	0	70	34	....	+12	91.0 88.4	1.63	29.0
18	44	Arteriosclerotic and hypertensive heart disease	130/100	++	+++	0	57	44	8.5	— 7	110.0 112.0	1.11	21.0
19	67	Syphilitic and arteriosclerotic heart disease with aortic insufficiency	140/ 50	++	++	++	71	39	....	—13	94.0 80.0	1.21	25.0
20	50	Arteriosclerotic and hypertensive heart disease	160/130	++++	++++	++++	36	52	....	+11 ?	120.0 111.0	1.45 ?	21.0

* D indicates decholin; S indicates saccharine; in all other cases sodium cyanide was used.
† The question mark indicates that edema prevented precise determination of the body surface.
‡ The two values are the differences between samples 1 and 2 and 2 and 3, respectively.

1.52 ± 0.06 liters per square meter per minute. The coefficient of variability was 27.3 per cent. The reference to the ratio between the means and their respective probable errors indicates that both samples were large enough to afford stable means.

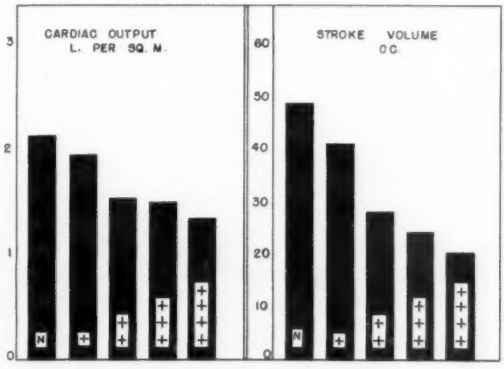

Chart 1.—The cardiac output and stroke volume as related to the degree of congestive heart failure. *N* indicates the normal group; plus signs indicate the degree of heart failure.

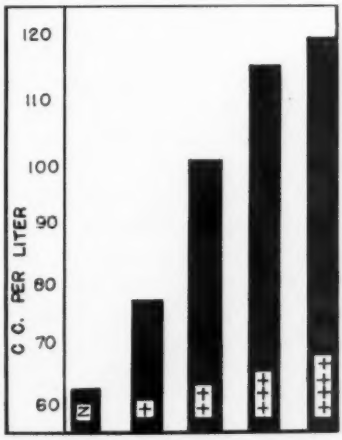

Chart 2.—The arteriovenous oxygen difference as related to the degree of congestive heart failure. *N* indicates the normal group; plus signs indicate the degree of heart failure.

The difference between the two groups, 0.64 ± 0.072 liters per square meter of body surface, is a statistically significant difference—about nine times its own probable error.

* D indicates dechalin; S indicates saccharine; in all other cases sodium cyanide was used.
† The question mark indicates that edema prevented probe determination of the body surface.
‡ The two values are the differences between samples 1 and 2 and 3 and 4, respectively.

The output per beat (stroke volume) for the subjects with decompensation was reduced, averaging 27 cc., while for the control subjects the average stroke volume was 49 cc.

While no sharp differentiation was observed among the patients with severe failure, the average values for cardiac output steadily diminished as the degree of failure increased. In the control group the output per square meter per minute averaged 2.1 liters; in the group with 1 plus failure, 1.88 liters; in the 2 plus group, 1.48 liters; in the 3 plus group, 1.44 liters, and in the 4 plus group, 1.34 liters.

Likewise, a decrease in stroke volume was observed with progressive increase in the gradation of failure. In the control group the average output per beat was 49 cc.; in the 1 plus group, 41 cc.; in the 2 plus group, 28 cc.; in the 3 plus group, 24 cc., and in the 4 plus group, 21 cc.

These data are illustrated by chart 1.

In the control subjects the average arteriovenous oxygen difference was 62.2 cc. per liter, while in the 1 plus group of patients with cardiac disease the average value was 76.3, in the 2 plus group 100, in the 3 plus group 114 and in the 4 plus group 118 cc. per liter. These results are indicated graphically in chart 2.

COMMENT

In this series of 20 patients with decompensation there was a trend toward decreased cardiac output in the patients with congestive failure when considered from the standpoint of output per square meter of body surface; this was even more striking when related to output per beat. The feeble pulsations of the hearts of the patients with a small cardiac output as seen by fluoroscopic examination afforded convincing visual proof of the low values. The increasing arteriovenous oxygen difference in the patients with more severe decompensation is likewise significant and is further evidence of the sluggish circulation of these patients.

From statistical analysis no smooth correlation between the level of the cardiac output and the degree of decompensation was observed. At the extremes—that is, in the 1 plus group and the 4 plus group—there was the definite suggestion of relation between the clinical state of the patient, on the one hand, and the level of the cardiac output and the arteriovenous oxygen difference on the other.

In only 1 case (case 7) was the cardiac output normal in the presence of congestive failure. The fact that overlapping of subnormal and normal values occasionally occurs is not surprising, since several factors which cause an increase in the cardiac output of normal persons are frequently present in association with cardiac decompensation: (1) exercise associated with hyperpnea, (2) the excitement and anxiety often present with severe decompensation, (3) long standing anoxemia of the tissues, (4) increased metabolism, (5) increased venous pressure and

(6) low grade fever. Thus several factors of importance in elevating the cardiac output are often operating simultaneously in many patients with decompensation. Yet, despite these stimuli, the cardiac output tends to be subnormal. In other words, because of the physical exercise associated with hyperpnea we doubt the truly "basal" state of the patients with cardiac decompensation and therefore believe that the low values for the majority of these patients are even more significant than our results indicate.

From personal communication with other physicians interested in the relation of congestive heart failure to the cardiac output, it is our opinion that the cases of 3 plus and 4 plus failure studied in this series may represent instances of more advanced myocardial damage than those in a previous series.[13] For this reason the lack of complete agreement with another report [14] may indicate a difference in selection of patients rather than differing results with similar technic.

SUMMARY

In 19 of 20 cases of congestive heart failure the cardiac output was subnormal, the mean value being 1.52 ± 0.06 liters per square meter per minute, while in control cases the mean was 2.16 ± 0.03 liters.

In the groups of patients with congestive failure of varying severity there was a trend toward reduction of cardiac output with the severer manifestations of failure.

13. Harrison, T. R.: Personal communication to the authors.

14. Harrison, T. R.; Friedman, B.; Clark, G., and Resnik, H.: The Cardiac Output in Relation to Cardiac Failure, Arch. Int. Med. **54**:239 (Aug.) 1934.

SPONTANEOUS ARTERIOVENOUS ANEURYSMS OF THE THORAX

A REVIEW OF THE LITERATURE, WITH A REPORT OF TWO CASES

EUGENE L. ARMSTRONG, M.D.

CHARLES B. COGGIN, M.D.

AND

HERMAN S. HENDRICKSON, M.D.

LOS ANGELES

Beevor, in 1832, was the first to describe spontaneous arteriovenous aneurysm of the thorax. Since that time there have been but two comprehensive reviews of the reported cases, Pepper and Griffith making the first, in 1890. These authors not only collected reports of 28 cases and added 1 of their own but laid down diagnostic criteria that have never been surpassed. In 1925 the second detailed review appeared, when Shennan reported 2 cases of his own and collected reports of 72 others. In the latter report a short summary of each case was given whenever the clinical record was accessible.

Since 1925 a number of authors have reported cases, with references to the literature, bringing the total number of cases to 98. We are adding 2 cases of our own and reports of 79 others in which the records are available, 24 of which were not included in either previous analysis.

The fact that only 2 cases of spontaneous arteriovenous aneurysm of the thorax have been discovered at the Los Angeles County Hospital in 19,000 autopsies further emphasizes the rarity of this condition. In addition, 1 case was reported from this hospital in 1935 by W. E. Graham and Samuel Weisross, the autopsy having been performed by the county coroner. A total of 192 cases of aneurysm of the aorta were found among the 19,000 autopsy reports mentioned, 144 of the patients having syphilis and 48 having arteriosclerosis.

SUMMARY OF CASES

Age and Sex.—The age and sex were mentioned in 80 of the 81 cases in which the records were accessible. The age incidence according to decades was as follows:

From the Department of Medicine of the College of Medical Evangelists and from the Los Angeles County Hospital.

Decades	Men	Women
20-30	1	0
30-40	13	0
40-50	21	4
50-60	30	3
60-70	7	1
Total	72	8—80

As expected, the majority of the patients were men, only 10 per cent being women. The greatest age incidence was between 50 and 60 years, 40 per cent of the patients being in this age group, while 72 per cent were between 40 and 60 years of age.

Etiologic Factors.—The data relative to the etiologic factors are as follows:

1. Syphilis
   (*a*) History only (26 cases)
   (*b*) Positive serologic evidence (11 cases)
   (*c*) Autopsy evidence (9 cases)
   (*d*) Doubtful evidence (9 cases)
2. Arteriosclerosis, rheumatic fever and typhoid were mentioned as possible causes

We feel that the percentage of cases of aneurysm due to syphilis is too low (less than 50 per cent) because of the fact that serologic tests have been in use only since 1906. Another factor is that many patients died before an adequate history and laboratory tests could be obtained. It is interesting to note that since 1925 reports of 26 cases have been collected, in 20 of which (77 per cent) there was definite evidence of syphilis, either serologically or anatomically. In this group of 26 cases, there was no autopsy in 2 cases and no access to the records in 1 case. Not including these 3 cases, there was positive evidence of syphilis in 87 per cent of the cases.

Exciting Cause of the Perforation.—Evidence indicates that physical strain and emotional stress or agitation are the exciting causes of perforation in a large number of cases. It is also true that there are a few cases in which neither of these is a factor.

Symptoms and Physical Signs.—There were 80 cases in which the symptoms and signs were mentioned:

Symptoms and Signs	Number of Cases
Cyanosis	80
Swelling	79
Suddenness of onset	50
Dyspnea	35

Symptoms and Signs	Number of Cases
Unconsciousness	16
Pain	15
Orthopnea	9
Tightness of neck and head	8
Dysphagia	6

Cyanosis and swelling limited to the distribution of the tributaries of the superior vena cava were constant findings. One patient died before swelling could develop. There was suddenness of onset in 62 per cent of the cases, making this an important point in the differential diagnosis.

On physical examination a large number of patients showed evidence of tumor in the thorax, that is, dulness below the right clavicle and behind the upper portion of the sternum. Occasionally a thrill was detected in this area. The veins over the thorax and abdomen were enlarged in 44 cases. Pulsation was noted in 12.

Cardiac murmurs were mentioned 77 times. In 30 cases the characteristic murmur was found, in 22 a double murmur, in 18 a systolic murmur alone and in only 1 a diastolic murmur. There were no murmurs in 6 cases. Either the characteristic murmur or a double murmur marked 67 per cent of the cases.

Length of Survival After Perforation.—The data regarding survival after perforation were as follows:

Survival	Number of Cases	Survival	Number of Cases
Immediate death	3	Up to 1 week	24
Less than 12 hours	4	1 week to 1 month	30
Less than 24 hours	5	1-2 months	14
1-2 days	2	Over 2 months	13
2-3 days	2		—
3-7 days	8	Total	81
		Recovery (patient alive at time of report; cases 20, 60, 97)	3

Position of Perforation; Relation to Azygos Vein; Size of Aneurysm.—In 81 cases the perforation was discussed. Perforations were double in 7 of these and triple in 3 others.

The relation of the perforation to the azygos vein was mentioned in 73 cases. In 41 cases the perforation was above the azygos vein, and in 4 of these it was in the terminal part of the innominate vein. Nine perforations were opposite the opening of the azygos vein, 18 were between the azygos vein and the right auricle and 2 were at the entrance to the auricle; in 3 cases the communication was with the right auricle. In those cases in which the perforation was above the azygos vein, the swelling and cyanosis were more or less limited to the head, neck and upper extremities; whereas in those cases in which it was

below or opposite the azygos vein, there were, in addition, swelling of the walls of the thorax and hydrothorax, with late extension to the lower extremities.

The average diameter of the aneurysm was about 8 cm. The smallest measured about 4.5 by 5 cm., and the largest was 16 cm. in diameter. The origin was in the ascending arch of the aorta.

Treatment.—The only treatment is symptomatic and supportive, in the attempt to maintain life until collateral circulation can be established. This evidently occurred in the 3 patients who are reported as having recovered or as still living.

Fig. 1 (case 1).—Infra-red photograph taken about one week before death. The edema and cyanosis, ending at the costal margin in a collar of venules, with the development of collateral circulation, are apparent.

CASE REPORTS

CASE 1.—Mr. T. J. B., aged 58, single, a Caucasian, was admitted to the Los Angeles County Hospital on Feb. 13, 1936. He complained of inability to sleep on his left side and back and precordial pain radiating to the left shoulder and arm for three years. For three weeks he had noted swelling and cyanosis of the face and neck.

History.—The patient first had difficulty in sleeping when lying flat on his back or on his left side. This symptom was gradual in onset and had progressed to the point where it was impossible for him to sleep unless he sat upright in bed. Almost simultaneously with the appearance of positional insomnia, the patient began to notice pain in the precordial region, which at first was brought on by

exertion and which radiated to the shoulder and arm. This condition gradually became worse, so that at the time of entry he felt pain with the slightest exertion. A sense of tightness in the throat associated with swelling and cyanosis of the head and neck had developed three weeks prior to entry. This gradually produced dyspnea. The cyanosis was limited to the head, neck and thorax.

The past history was essentially unimportant with the exception of a penile chancre, which occurred when he was 28 and which had been inadequately treated. The family history was not significant.

Physical Examination.—Physical examination revealed a well developed and well nourished man in an orthopneic position. He was dyspneic and exhibited marked cyanosis and swelling of the face, neck and thorax. The temperature was 98 F., the pulse rate 88 and the respiratory rate 20. He weighed 165 pounds (74.8 Kg.) and was 67 inches (170.18 cm.) tall. The pupils were equal and reacted to light and on convergence. The fundi were normal except for dilated vessels and cyanosis. The ears showed cyanosis but no changes in the tympanic membrane. There was marked congestion of the pharynx and nasal passages, with cyanosis of the mucous membrane. The teeth were carious. The tonsils were small and buried. The neck was swollen, tense and cyanotic, with pitting on pressure, which was more marked on the right side. There were no pulsating vessels. The chest showed cyanosis and swelling, which extended to the costal margin, ending in a collar of distended venules. The left border of cardiac dulness was found to be in the fifth interspace at the midclavicular line. The right border was 3 or 4 cm. to the right of the sternum in the second intercostal space. The cardiac rhythm was regular. A loud systolic murmur was heard best at the second interspace on the right; a diastolic murmur was heard over the same area. The blood pressure in the left arm was 150 systolic and 30 diastolic; in the left leg, 180 systolic and 50 diastolic; in the right arm, 145 systolic and 30 diastolic, and in the right leg, 200 systolic and 55 diastolic. The pulse was of the Corrigan type. A pistol shot and the Duroziez sign were heard over the femoral arteries. Examination of the lungs and abdomen revealed no abnormality. Cyanosis and edema were noted in both upper extremities, being more marked in the right than in the left. The lower extremities were normal. Neurologic and glandular examinations revealed normal conditions.

Laboratory Examination.—The Wassermann and Kahn tests of the blood gave a positive reaction. Examination of the blood showed: erythrocytes, 4,100,000; hemoglobin, 65 per cent; leukocytes, 9,150; neutrophils, 76 per cent; lymphocytes, 20 per cent, and monocytes, 4 per cent. The urine was normal.

Roentgenographic Study.—The cardiac silhouette was essentially normal. There was an aneurysm of the ascending and transverse aorta, with marked enlargement of the ascending aorta. The pulmonary fields were clear.

Electrocardiographic Study.—Moderate slurring of the QRS complex was present in the standard leads. The voltage was low in leads I and III. Lead IV showed considerable slurring of the QRS, and the T wave tended to be diphasic. The conclusion was reached that there were myocardial impairment and coronary disease.

Clinical Diagnosis.—The clinical diagnosis was syphilitic heart disease and aneurysm of the ascending aorta, with compression of and perforation into the superior vena cava.

Course.—The patient's condition remained about the same except for increasing dyspnea and pain in the throat. Occasionally he awakened with a sensation of strangulation. The first marked change in his condition was noted on March 15,

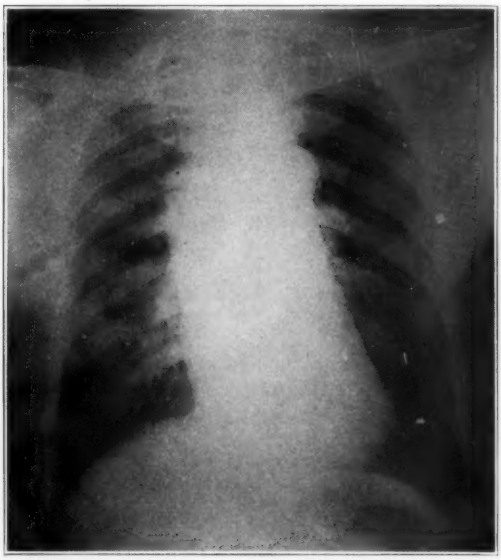

Fig. 2 (case 1).—Roentgenogram showing aneurysm of the ascending aorta.

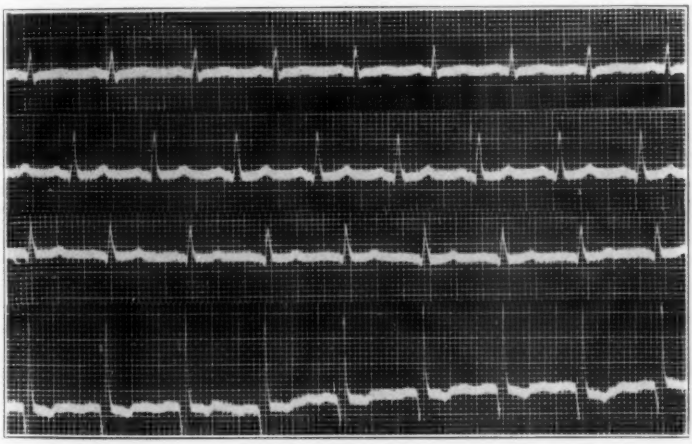

Fig. 3 (case 1).—Electrocardiogram taken with the patient lying down (resistance, 400 ohms; auricular rate, 110; ventricular rate, 110; PR interval, 0.16 second; rhythm, regular).

when he had a smothering attack; the cyanosis became more intense and the dyspnea more marked. From this time on it was necessary to give him oxygen. The following day it was noted that the veins over the abdomen were beginning to distend and to pulsate. The character of the cardiac murmur also changed, becoming louder and more whirring, so that it was continuous. On March 23 moist rales developed in the lungs. Because of the striking pulsation in the veins, Dr. R. Manning Clarke suggested the diagnosis of an arteriovenous communication. The pressure in the pulsating veins was measured and found to be 22 cm. of water, the water pulsating in the manometer 2 or 3 mm. The oxygen tension of the blood in the pulsating veins on the abdomen was 10.8 per cent and the tension in the veins of the lower extremities 10.4 per cent. These differences were not sufficient to be of significance. From March 28 to April 2 the patient rapidly grew worse, with the development of congestive heart failure, resulting in ascites, hydrothorax and extension of edema to dependent portions. During this time the patient failed to respond to any medication and died suddenly on April 2, while being moved about in bed.

The treatment administered was symptomatic, morphine, ice bags, digitalis and oxygen being used.

Autopsy.—An autopsy was performed by Dr. Albert F. Brown. There were marked generalized pitting edema and lividity above the level of the epigastrium. The pupils were equal and regular. The right testicle was slightly enlarged and indurated. Superficial veins were not visible. The skull and central nervous system were normal.

The heart weighed 390 Gm. The pericardial sac contained 50 cc. of clear fluid. The surfaces were smooth. The wall of the left ventricle was 14 mm. thick; that of the right ventricle, 6 mm. thick. Each chamber was moderately dilated. The circumference of the tricuspid valve was 12.5 cm.; that of the pulmonic valve, 9 cm. One of its cusps was held rigidly into the lumen of the valve because of the complete occupation of its sinus by a hemispherical aneurysm of the adjacent aorta, which was 1.5 cm. in diameter. The circumference of the aortic valve was 9 cm. Its cusps were not appreciably altered, and the commissures were not widened. There was no evidence of incompetency. The coronary orifices were 1 cm. above the upper margin of the valve. The left orifice was of normal caliber, while the right showed 50 per cent stenosis, beginning in the depths of a 5 mm. hemispherical pouch. The remaining portions of the coronary arteries were normal. The ascending aorta from immediately above the coronary mouths to the first part of the arch was diffusely aneurysmal, the circumference being 12 to 15 cm. Its wall was thick, and the intima revealed the pearly plaques and wrinkling of syphilitic aortitis. The dilatation was chiefly posterolateral (right). Two secondary pouches and one perforation characterized the aneurysm. These satellite sacs were each 1.5 cm. in diameter and hemispherical. One projected into the pulmonary valve, the other was in the anterior aspect of the aorta. The perforation, 12 mm. in diameter, was located 6 cm. above the aortic valve in the right posterolateral aspect. It opened directly into a localized intrapericardial sac, about 5 cm. long and 2 cm. in diameter, which lay between the aortic aneurysm and the superior vena cava, the latter vessel communicating with the pericardial pocket by means of a 7 mm. perforation. Neither the aortic aneurysm, except for the small secondary pouches, nor the pericardial sac contained antemortem thrombus, only soft, dark red clot. The vena cava, aside from the perforation, seemed essentially unchanged, but the innominate veins contained small, adherent plaques of thrombi. The tributaries of these veins which were examined, viz., both subclavian and both internal jugular veins, the cephalic veins and the pectoral

veins, were occluded by antemortem thrombi. The occlusion was complete except in the right internal jugular vein, where about 50 per cent of the lumen remained patent. The thrombotic material was a dull gray-red and somewhat granular and occasionally showed beginning degeneration. The azygos veins were free from thrombi. The descending aorta revealed little, if any, evidence of syphilitic involvement, and the inferior vena cava appeared normal.

The right pleural cavity contained 1,500 cc. and the left 1,200 cc. of clear, amber fluid. The specific gravity was 1.016. At the apex of the right lung an

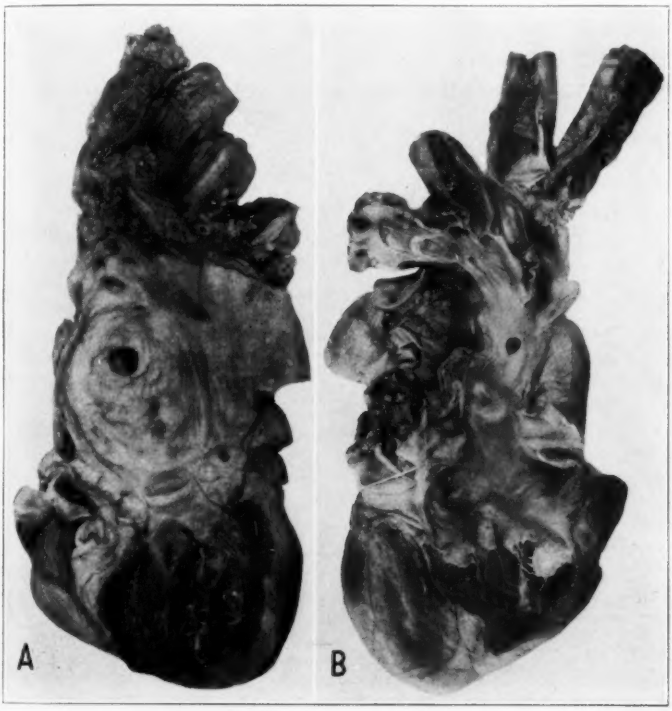

Fig. 4 (case 1).—*A*, the heart is opened on the aortic side, showing the aneurysm with the perforation and the pericardial pouch between the aorta and the vena cava. *B*, the heart is opened on the side of the vena cava, showing the perforation into the superior vena cava and the thrombi in its tributaries.

old fibrous subpleural scar and old fibrous adhesions were present. The right lung weighed 750 Gm. and the left lung 700 Gm. Each lung was edematous and posteriorly congested. The bronchial mucosa was slightly hyperemic. The lumen contained thin mucus. The pulmonary artery was normal.

The peritoneum and pancreas were normal. The peritoneal cavity contained 100 cc. of clear fluid. There was slight passive congestion of the liver. The spleen and kidneys were normal.

The right testis was slightly enlarged and firm. The cut surface showed replacement of the substance of the testis by firm, pale white, translucent tissue, which was confluently nodular. The left testicle was normal.

Examination of the skeletal system revealed that the bodies of the fourth to seventh dorsal vertebrae were eroded to a depth of 5 mm. on the right anterolateral aspect because of the pressure of the aneurysm.

Anatomic Diagnosis.—The anatomic diagnosis was: (1) syphilitic aortitis; (2) a ruptured fusiform aneurysm of the ascending aorta; (3) stenosis of the pulmonary valve due to encroachment of the aortic aneurysm; (4) localized hemopericardium; (5) a fistula involving the aorta, pericardium and vena cava; (6) thrombosis of the great veins of the neck and upper extremity, and (7) gumma of one testicle.

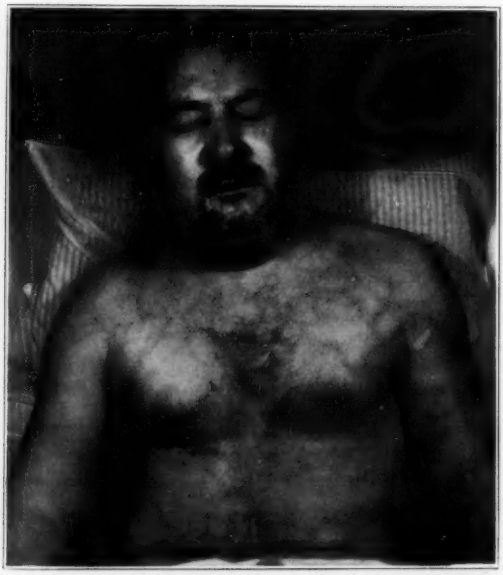

Fig. 5 (case 2).—Infra-red photograph showing the cyanosis and edema above the epigastrium, with the developing of the collateral circulation.

CASE 2.—Mr. J. R., aged 46, a Mexican, single, was admitted to the Los Angeles County Hospital on Feb. 24, 1937. He complained of a brassy, nonproductive cough, with hoarseness and orthopnea, for one year. Cyanosis and swelling had been noted for three months prior to entry.

History.—The patient was apparently well until one year before entry, when he acquired a brassy, nonproductive cough, with hoarseness, dyspnea and orthopnea but no fever. The cyanosis and swelling were first noticed three months before entry. They began in the right upper extremity and gradually extended to the head, neck, left upper extremity and thorax and down to the epigastrium and had increased in severity in the last four days.

A recent history revealed no abnormalities except the presenting illness. The patient had had gonorrhea and possibly chancre in his youth. The family history was not significant.

Physical Examination.—The patient was a well developed and well nourished man in an orthopneic position. There were cyanosis and swelling of the head, neck, upper extremities and thorax. The temperature was 98.6 F., the pulse rate 88 and the respiratory rate 18. He weighed 174 pounds (78.9 Kg.) and was 74 inches (188 cm.) tall. The pupils were equal, and their reactions were normal. Except for cyanosis and swelling the ears, nose and mouth were normal. The cyanosis and edema extended down to the costal margin. The chest was barrel shaped, and dilated veins were present both anteriorly and posteriorly. The right border of cardiac dulness extended to the right midclavicular line in the second interspace. The apex beat and point of maximum intensity were in the sixth interspace in the left nipple line. Whirring systolic and diastolic murmurs were heard just below and to the right of the aortic area. The systolic phase was louder and harsher than the diastolic. Examination of the lungs showed dulness to flatness over the base of the right lung, with distant breath sounds, which were bronchovesicular. Moist rales could be heard throughout the right pulmonary field. The left lung was normal. Abdominal examination disclosed only dilatation of the superficial veins. Although the upper extremities were cyanotic and edematous, the lower extremities were normal. Neurologic and glandular examinations revealed no abnormality.

Laboratory Examination.—A blood count disclosed: erythrocytes, 4,240,000; hemoglobin, 76 per cent; leukocytes, 5,150; neutrophils, 76 per cent; lymphocytes, 15 per cent; monocytes, 8 per cent, and eosinophils, 1 per cent. The Wassermann and Kahn tests of the blood gave a positive reaction. The urine showed a 2 plus reaction for albumin but contained no pus.

Roentgenographic Examination.—A large amount of abnormal density was seen in the lower part of the right pulmonary field, extending up along the lateral wall of the chest. A small amount of fluid was seen at the left costophrenic sulcus. The mediastinum at the level of the aortic arch was seen to be considerably expanded to the right; this expansion did not pulsate, and so far as could be ascertained through the fluid, it had the characteristics of a mediastinal tumor.

Electrocardiographic Examination.—The QRS complex was small and slurred in all leads. It was concluded that there was myocardial impairment.

Clinical Diagnosis.—The diagnosis was syphilitic aortic aneurysm perforating into the superior vena cava.

Course.—The treatment was symptomatic. The patient grew worse rapidly and on the second day in the hospital showed pulsating veins on the thorax. On the fourth day he became maniacal. He climbed out of bed and, seizing a chair, broke two windows; whereon he immediately dropped dead.

Autopsy.—Autopsy was performed by Dr. J. M. Shachtman. There were cyanosis and pitting edema of the body above the costal margin. The skull and central nervous system were not examined.

The heart was apparently not enlarged. The tricuspid valve measured 11.5 cm. in circumference. The leaflets were normal. The pulmonary valve measured 7.5 cm. in circumference and appeared normal. The mitral valve measured 7 cm. in circumference. The leaflets were thickened on the external margins and at the base. The chordae tendineae were thickened and shortened. The aortic valve measured 7 cm. in circumference, and between two of the cusps there was a

Fig. 6 (case 2).—Roentgenogram showing widening at the aortic area and fluid in the right side of the chest.

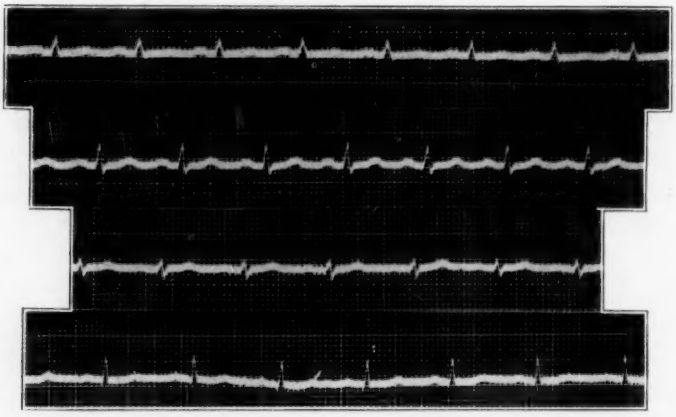

Fig. 7 (case 2).—Electrocardiogram taken with the patient reclining in bed (resistance, 400 ohms; auricular rate, 100; ventricular rate, 100; PR interval, 0.2 second; rhythm, regular).

marked amount of calcification. Between the other cusps the commissures were widened. The orifices of the coronary arteries appeared to be normal. In the ascending portion of the aorta on the posterior surface there was a large aneurysm filled with a clot. From this aneurysm there were a few outward pocketings. Two small openings were disclosed near the origin of the superior vena cava, where it had been perforated by the aneurysm. Below this the superior vena cava was constricted because of the pressure of the aneurysm. Anteriorly the bifurcation of the trachea seemed to be compressed.

About 2,000 cc. of serosanguineous fluid, containing a large amount of fibrin, was present in the right pleural cavity. The right lung weighed 350 Gm. and was atelectatic. The left lung weighed 350 Gm. and had a thickened pleura. Surfaces made by cutting showed congestion and were reddish gray.

The abdominal viscera were normal except for passive congestion.

Anatomic Diagnosis.—The anatomic diagnosis was: (1) syphilitic aortitis, (2) a ruptured aneurysm of the ascending aorta, (3) a fistula involving the aorta and vena cava, (4) acute congestive heart failure, (5) chronic rheumatic endocarditis and (6) pulmonary atelectasis, with pleural effusion.

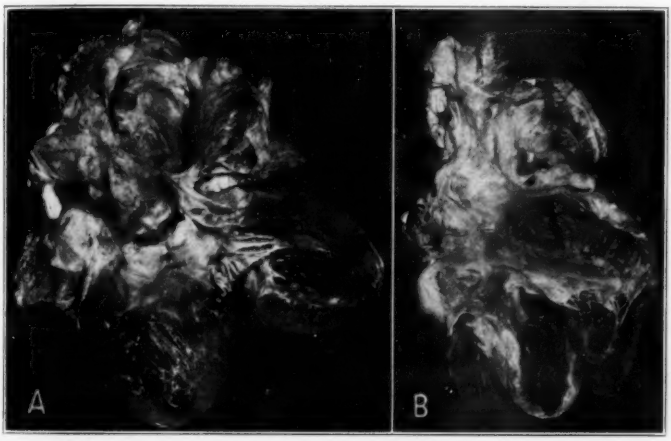

Fig. 8 (case 2).—*A*, the heart is opened on the aortic side, showing the aneurysm with two small openings. B, the heart is opened on the side of the vena cava, showing two small communications near the origin of the cava.

COMMENT

Pepper and Griffith, in 1890, called attention to four principal diagnostic signs and symptoms. These are:

1. Cyanosis, edema, coldness and distention of the veins of the upper part of the body, with other evidence of obstruction of the circulation of blood in the tributaries of the superior vena cava. They stated that these signs may appear over all the body above the waist line or may be limited to certain parts. The face and neck are almost invariably

affected, but the arms, shoulders and thorax may or may not be involved. Sometimes the changes are unilateral. These variations depend on the location of the perforation in the vena cava, that is, whether it is above or below the azygos vein, and the extent of the compression of the vena cava by the aneurysm. The cyanosis is the result of the impeded venous return, consequent to pressure on and within the vena cava, rather than the result of mixture of arterial and venous blood. Dyspnea may be due to compression of the trachea by the aneurysmal mass, to edema of the larynx or lungs or to hydrothorax.

2. Suddenness of onset of symptoms. The onset of symptoms has taken place under various states of rest and activity but has been sudden in 62 per cent of the cases.

3. Evidence from physical examination of tumor in the thorax and the probability that it is aneurysmal. Roentgenographic examination confirms the diagnosis in many cases.

4. Existence of a murmur characteristic of a communication between an artery and a vein. The murmur was first described, by Dr. James Hope,[1] as a "continuous murmur augmented in intensity during the ventricular systole and diastole and in both attended with a great degree of purring tremor." Thurnam,[2] in 1840, described the murmur as a "superficial, harsh, and peculiarly intense swaying or blowing sound accompanied by an equally marked purring tremor, heard over the varicose orifice, and in the current of circulation beyond it; this sound is continuous, but is loudest during the systole, less loud during the diastole, and still less so during the interval."

In addition to these four diagnostic criteria of Pepper and Griffith, Klinck (1936) mentioned the hepatic pulsation which had been observed by Hoover and Beams[3] in several cases of fistula between the femoral artery and the vein, as well as in cases of a communication between the carotid and the jugular vein. That a pulsating liver may be found in some cases of fistula involving the aorta and the vena cava is not doubted, although it is strange that this has previously been overlooked. Hoover and Beams stated that the arteriovenous leak alone does not produce the hepatic pulsation until the caval pressure increases as a result of the incompetence of the heart caused by the fistula.

We should like to emphasize the diagnostic importance of pulsation of superficial veins. This was present in both of our cases and was

1. Hope, James: A Treatise on the Diseases of the Heart, ed. 3, London, J. Churchill, 1839; quoted by T. Shennan (1925).

2. Thurnam, cited by T. Shennan (1925).

3. Hoover, C. F., and Beams, A. J.: The Diagnosis and Pathologic Physiology of Arteriovenous Aneurisms, Arch. Int. Med. **33**:1 (Jan.) 1924.

responsible for the making of the correct diagnosis. Pulsation of veins was mentioned in only 10 other cases, but we believe that it probably occurred more often.

Another interesting observation was the presence of the sign of Hall and Rowlands. Leonard Hill,[4] working with Rowlands and others, reported in 1912 on his observations with blood pressure readings for the arms and legs. He noted that normal persons in a reclining position had no marked change in blood pressure in the arms and legs. In cases of aortic regurgitation, however, the pressure in the legs was increased over that in the arms. In 1923 Lewis and Drury[5] showed clinically in 5 cases of arteriovenous aneurysm resulting from war injuries and experimentally after operations on dogs that arteriovenous aneurysm or side to side anastomosis resulted in a lowering of the diastolic pressure, a water hammer pulse, an increase in the blood pressure in the leg over that in the arm (Hall and Rowlands sign of differential blood pressure in the arm and leg), capillary pulsation, increased cardiac rate and other manifestations—the hydrodynamic phenomena of aortic regurgitation. This was true in 1 of our cases in which the blood pressure had been recorded for both legs and arms.

The condition must be differentiated from other obstructions of the superior vena cava. Cases of obstruction due to compression and thrombosis are at times almost impossible to differentiate from cases of arteriovenous fistula. The severe edema and cyanosis, limited sharply to the upper part of the body, seem to be more or less characteristic of fistula, whereas the alterations may not be so extreme with other obstructions, because the conditions are more favorable for the formation of collateral circulation. The characteristic murmur is a helpful sign. It has been reported in cases of obstruction, but in the presence of this finding there is much more likely to be a fistula. The systolic pulsation of the veins is probably the most accurate sign of a varicose aneurysm; it has been absent more often than present. Signs of aortic regurgitation, with the blood pressure in the leg greater than that in the arm, are suggestive.

SUMMARY

1. A review of the literature and the history and findings in 2 cases of fistula involving the aorta and vena cava are presented.

2. The diagnostic criteria are discussed.

3. The presence of pulsating superficial veins is emphasized as it establishes the diagnosis.

4. Hill, L.: The Sphygmomanometer in General Practice, Lancet **182**:1406, 1912.

5. Lewis, T., and Drury, A. N.: Observations Relating to Arteriovenous Aneurism, Heart **10**:301 (Oct.) 1923.

4. The presence of the sign of Hall and Rowlands (an increase in the blood pressure in the leg over that in the arm) is noted as a suggestive aid in the diagnosis of arteriovenous fistula.

Dr. Newton Evans, Chief of the Department of Pathology, gave us permission to use the autopsy material; William F. Davis supplied the photographs, and Mrs. Ella Moyers and Esther Young helped collect the material for the bibliography.

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BUNDLE BRANCH BLOCK

CRITERIA OF CLASSIFICATION, DIAGNOSIS AND PROGNOSIS; A STUDY OF TWO HUNDRED AND TEN CASES, WITH FOLLOW-UP DATA

HUGO A. FREUND, M.D.
Chief of Department of Internal Medicine, Harper Hospital
AND
RAYMOND SOKOLOV, M.D.
Resident in Medicine, Harper Hospital
DETROIT

Since Eppinger and Rothberger, in 1910, reported their experimental work on dogs in which the right and left branches of the His bundle were severed, a large volume of literature on this subject has accumulated. In recent years several workers have analyzed case records in an effort to determine what if any are the prognostic implications of electrocardiographic evidence of bundle branch block. Among the more recent of these surveys have been those of Willius,[1] King,[2] Wood,[3] Graybiel and Sprague[4] and Sampson and Nagle.[5] In 1934 Wilson and his co-workers,[6] experimenting with serial precordial leads for human beings and with curves obtained after section of the right bundle branch in dogs, were able to show that certain electrocardiographic patterns, previously not fully understood, represented right bundle branch block in man. These workers[7] described "electrocardiograms of an unusual type" which also were thought to be representative of right bundle branch block. Shortly afterward Bayley,[8] using Wilson's criteria for the diagnosis of right bundle branch block, subdivided all his cases into four groups, the basis of the subdivision being variations in the configuration of the QRS complex.

If Wilson's conclusions are accepted, the diagnosis of bundle branch block will be made more frequently than has been done in the past.

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Furthermore, with the inclusion of more cases in this group, especially those of a type previously not included, it might become more imperative to alter somewhat the usual opinion with regard to the prognosis when this lesion is present.

SELECTION OF CASES

We have reviewed all the cardiograms taken at Harper Hospital and in the private practice of one of us over a ten year period (1927 to 1936) along with the case records. The curves have been reread in the light of the newer criteria. In 179 (85.2 per cent) of the 210 cases of bundle branch block in this series, follow-up information has been obtained. In 64.4 per cent of these cases the patient was seen in private practice; the remainder (35.4 per cent) were semicharity or charity patients. Only 17.7 per cent were outpatients; the others were hospitalized.

CLASSIFICATION

Our cases of bundle branch block have been divided into four main groups. In group 1 were included all those believed to be cases of complete left bundle branch block. We have differentiated between heterophasic and homophasic left bundle branch block, as suggested by Graybiel and Sprague.[4] Heterophasic left bundle branch block (group 1a) is represented by the classic "levogram." All the tracings for this group of cases had a QRS interval of 0.12 second or more. The QRS complex was frequently notched, the T wave was exaggerated and pointed in a direction opposite to the main deflection of the QRS complex and, finally, the main deflection of the QRS complex was directed upward in lead I and downward in lead III (fig. 1). Eighty cases fell into this group. In the cases in group 1b, cases of homophasic left bundle branch block, the tracing differed from the heterophasic type only in that the T wave was directed upward in lead I and downward in lead III. We had 10 such cases (fig. 2).

Group 2 included cases of complete right bundle branch block. Its subdivisions were patterned after Bayley's[5] scheme. In the cases in group 2a there was the classic "dextrogram" (fig. 3). "In lead I the chief initial deflection is a broad downward excursion, S, which is preceded by a smaller upward movement, R. T_1 is upright. In lead III, the chief initial deflection is a broad, notched, upward excursion, R, which is preceded by a smaller dip, Q. T_3 is inverted." The QRS interval in every instance was 0.12 second or more. Fourteen of our cases belonged in this group.

Eighteen cases were placed in group 2b (fig. 4). The tracings in these cases differed from those in the preceding group of cases only in that R in lead I had a greater amplitude than S.

Group 2c included 21 cases (fig. 5). Lead I of the tracings in this group of cases resembled lead I in the tracings in the cases in group 2b: however, in lead III the most conspicuous QRS deflection was a narrow inverted spike followed by a broad upright summit.

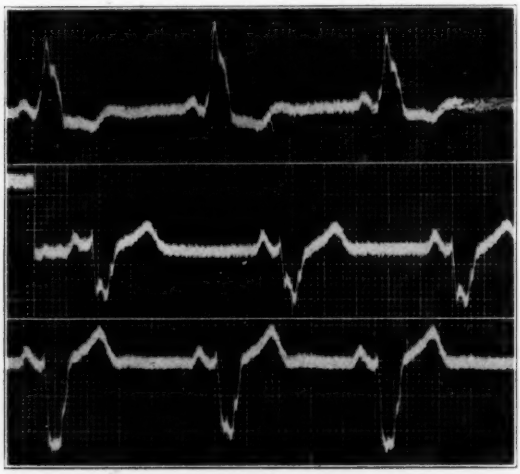

Fig. 1.—Left bundle branch block, heterophasic, of type 1a. The QRS interval, 0.16 second, is notched and slurred in all leads. The T wave is prominent and opposite to the main deflection of the QRS complex. The main deflection of QRS is directed upward in lead I and downward in lead III.

Fig. 2.—Left bundle branch block, homophasic, of type 1 b. The QRS interval, 0.14 second, is notched and slurred in all leads. The main deflection of QRS is directed upward in lead I and downward in lead III. The T wave is in the same direction as the main deflection of QRS.

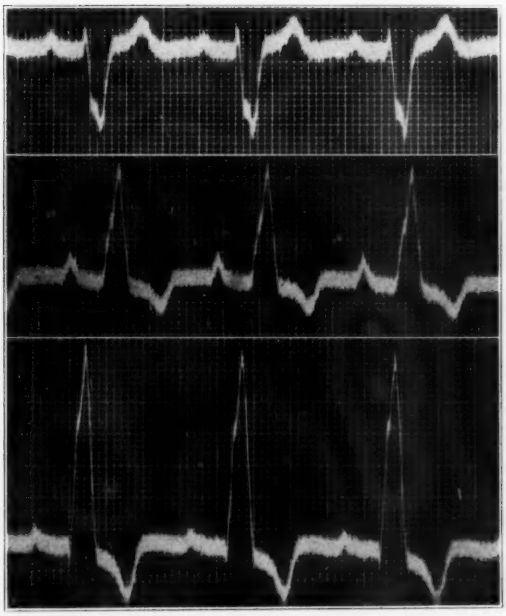

Fig. 3.—Right bundle branch block of type 2a. The QRS interval, 0.15 second, is notched and slurred in the first two leads and slurred in lead III. The T wave is prominent and points in a direction opposite to the main deflection of QRS. The main deflection of QRS is directed downward in lead I and upward in lead III. In lead I the chief initial deflection is a broad downward excursion, S, which is preceded by a smaller upward movement, R. In lead III the chief initial deflection is a broad upward excursion, R, which is preceded by a smaller dip, Q.

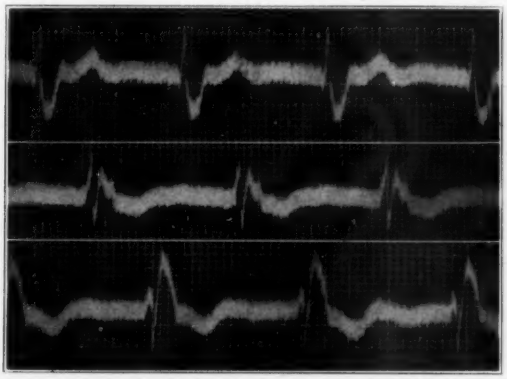

Fig. 4.—Right bundle branch block of type 2b. The QRS interval, 0.16 second, is notched and slurred in all leads. In lead I there is a broad downward excursion, S, which is preceded by a steep upward spike. The amplitude of R in lead I is greater than that of S. In lead III the main deflection of QRS is directed upward. The T wave is in a direction opposite to the main deflection of QRS.

In the 6 cases in group 2d the tracing differed from that in the previous group of cases only in that it lacked the broad upward summit in lead III (fig. 6). It will be noted that two features were common to all four types of right bundle branch block, namely, a QRS interval of 0.12 second or more and a deep, broad downward deflection, S, in lead I.

Group 2e was reserved for those cases in which the curves were similar to those described by Wilson [7] as "electrocardiograms of an unusual type" and said by him to represent right bundle branch block (fig. 7). In these curves the amplitude of all the deflections in lead I was small, there was a conspicuous S deflection and T was flat or upright. Leads II and III resembled those seen in cases of left bundle

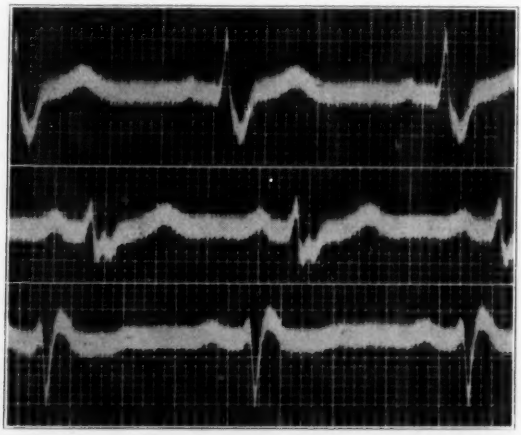

Fig. 5.—Right bundle branch block of type 2c. The QRS interval, 0.15 second, is notched in lead II and slurred in all leads. In lead I there is a broad downward excursion, S, preceded by a sharp spike, R. The amplitude of R is greater than that of S. In lead III the most conspicuous QRS deflection is a narrow inverted spike followed by a broad upward summit.

branch block. Wilson stated that this type of curve is probably not common but that its frequency is not known. In our series, 3 cases were found in which this type of tracing was obtained. A fourth curve showing similar characteristics was discovered as a terminal feature in a case which had previously belonged in group 4.

Group 3 consisted of 7 cases in which the disorder was difficult to classify. In all the cases the QRS interval was 0.12 second or more. In most of these cases there were all the criteria necessary for the diagnosis of bundle branch block, but localization characteristics were lacking. For example, figure 8 exhibits the curve in a case in which QRS was similarly directed in leads I and III.

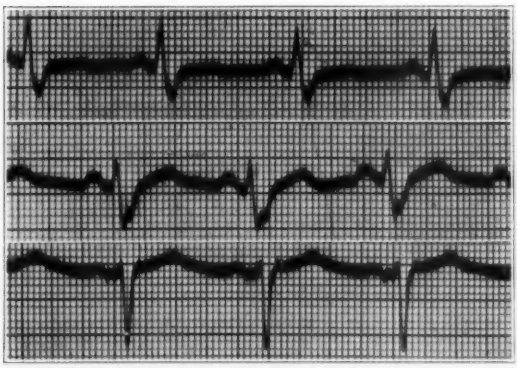

Fig. 6.—Right bundle branch block of type 2 d. The QRS interval, 0.14 second, is notched and slurred in the first two leads. In lead I there is a deep, broad downward deflection, S, preceded by an upward spike, R. In lead III the main deflection of QRS is directed downward and is not followed by an upright summit.

Fig. 7.—Right bundle branch block of type 2 e. The QRS interval, 0.16 second, is notched in all leads. In lead I the amplitude of all deflections is small, there is a conspicuous S deflection and T is flat or upright. The tracings in leads II and III resemble those seen in cases of left bundle branch block.

Group 4 consisted of cases in which the curves exhibited intraventricular conduction defects. There were included all the curves conforming to the type first described by Oppenheimer and Rothschild [9] as representative of arborization block. As such they were characterized by a QRS interval exceeding 0.1 second, notching of the R wave, low voltage in all three leads and absence of the typical diphasic curve with a huge T wave found in cases of bundle branch block (fig. 9). In this last group were included cases in which there were other curves in which the QRS interval exceeded 0.12 second but which lacked the distinguishing features of any of the previously described types. Fifty fell into this group of cases of heterogeneous type.

The ratio of the incidence of left bundle branch block to right bundle branch block was 90 to 63. This is comparable to the 103 to

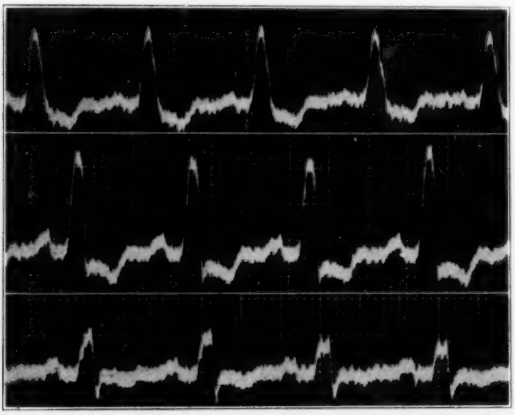

Fig. 8.—Bundle branch block of indefinite localization. The QRS interval, 0.13 second, is notched in leads II and III. The main deflection of QRS is directed upward in all three leads.

70 ratio in Bayley's [8] series and represents a higher incidence of right bundle branch block than that reported by other investigators. Graybiel and Sprague [4] found 125 cases of left bundle branch block as compared with 29 cases of right bundle branch block.

DISTRIBUTION

Sex.—There were 126 (60 per cent) males and 84 (40 per cent) females.

Race.—All but 5 (3 Negroes, 1 Filipino and 1 Japanese) of the total number of patients were of the white race.

9. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes with Myocardial Involvement, J. A. M. A. **69**:429, 1917.

Age.—The largest number of cases occurred in patients in the sixth and seventh decades. The youngest patient was 4½ years old and the oldest 82. Table 1 shows the age distribution for the various groups.

Etiology.—No attempt was made to separate the arteriosclerotic from the hypertensive patients; together they accounted for 76.6 per cent of all the patients. Rheumatic heart disease was the probable cause in 9.5 per cent. The highest percentage of rheumatic and congenital heart disease occurred in the cases in group 2 (right bundle branch block). Table 1 shows the distribution of cases with respect to the chief etiologic factors.

ASSOCIATED FINDINGS

General Condition of the Patient.—In 202 of the 210 cases there was sufficient information in the record to permit approximate evalua-

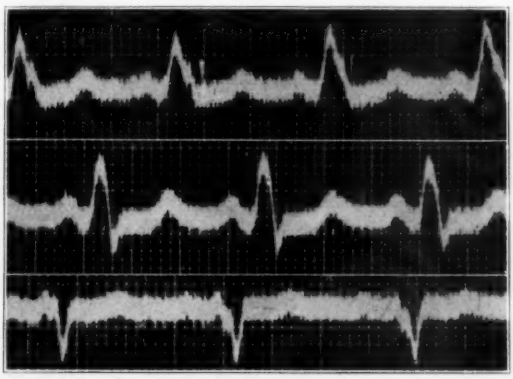

Fig. 9.—An intraventricular conduction defect of lesser degree (type 4). The QRS interval, 0.14 second, is notched and slurred in all leads. There is low voltage in all three leads. The T wave is conspicuous, and the deflection is not opposite to that of QRS.

tion of the patient's general condition at the time the diagnosis of bundle branch block was made. In 64 cases (31.6 per cent) the condition was considered good; that is, there was no evidence clinically of any cardiac embarrassment or any history of previous cardiac decompensation. In 83 cases (41 per cent) the patients were regarded as having been in fair condition, having shown symptoms relative to their cardiovascular system or signs of limited cardiac reserve but no evidence or only slight evidence of cardiac failure. In 55 cases (27.2 per cent) the patients presented definite evidence of cardiac failure when first seen; these were classified as being in poor condition. Twenty-one were in a terminal condition when brought into the hospital and were dead within a few days.

Valvular Disease.—In 32 cases a diagnosis of valvular heart disease was made. Twelve were mitral lesions, 11 were aortic, 6 were combined aortic and mitral and 3 were congenital.

Associated Arrhythmias.—The most frequently encountered arrhythmia in patients with bundle branch block is auricular fibrillation. It occurred in 29 cases (13.8 per cent). It appears to be proportionately

TABLE 1.—*Distribution of Cases*

		Group 1	Group 2	Group 3	Group 4	Total
Age	0- 9	0	1	0	0	1
	10-19	0	3	0	2	5
	20-29	2	3	0	0	5
	30-39	2	1	2	7	12
	40-49	12	10	2	11	35
	50-59	25	13	2	11	51
	60-69	31	20	0	13	64
	70-79	13	10	1	5	29
	80-89	2	1	0	1	4
Sex	Male	48	38	5	35	126
	Female	42	25	2	15	84
Etiologic factors	Arteriosclerosis	68	47	6	40	161
	Rheumatic fever	8	7	0	5	20
	Syphilis	5	1	1	2	9
	Thyroid disorder	6	1	0	1	8
	Congenital condition	0	3	0	0	3
	Miscellaneous conditions	1	2	0	2	5

TABLE 2.—*Associated Data* *

	Group 1	Group 2	Group 3	Group 4	Total	Percentage
Number of cases	90	63	7	50	210	....
Cardiac enlargement	71	40	6	38	155	74.0
Cardiac failure	65	28	2	27	117	57.0
Previous history of heart disease	61	28	2	26	117	58.0
Bedridden	28	15	1	17	61	29.1
Ambulatory	52	40	6	31	129	61.7
Partially bedridden	10	7	0	2	19	9.0
Coronary thrombosis	15	8	1	7	31	15.0
Reduplication of apical second sound	2	0	0	0	2	1.0
Gallop rhythm	8	3	0	8	19	9.2
Angina	21	9	1	8	39	18.9
Distant heart sounds	36	14	4	20	74	35.9
Auriculoventricular delay	11	10	1	3	25	11.9
Auriculoventricular dissociation	6	2	1	2	11	5.2
Auricular fibrillation	12	8	0	9	29	13.8

* Some of the records were not complete in every respect. When information was lacking on a particular point, that case was not included in the totals and percentages. This will explain certain apparent mathematical discrepancies in this table.

distributed among the four major types of bundle branch block. Auriculoventricular delay, as evidenced by prolongation of the PR interval beyond 0.2 second, was noted in 25 cases (11.9 per cent). Auriculoventricular dissociation occurred in 11 cases (5.2 per cent). Gallop rhythm was detected in 19 cases (9.2 per cent), but this was probably not always carefully searched for. Other arrhythmias present were ventricular tachycardia, 3 cases; paroxysmal auricular tachycardia, 2 cases; auricular flutter, 3 cases, and pulsus alternans, 2 cases.

Previous History of Heart Disease.—It is surprising how many patients with bundle branch block give no history referable to the heart. In this series 58 per cent of the patients had had cardiac symptoms. However, many of these had noted merely dyspnea on exertion or had a minor complaint not at all incompatible with their age. Angina pectoris was reported by 18 per cent. Many patients of the entire group did not show cardiac symptoms until some terminal situation arose.

Cardiac Enlargement.—The heart was found to be enlarged to percussion in 155 cases (74 per cent); this was confirmed by roentgen examination in 66 cases. In the remaining 26 per cent the heart was not significantly enlarged.

Cardiac Failure.—In 117 cases (55.5 per cent) there were either physical signs of cardiac decompensation or else a history of previous decompensation. In many of these cases the evidences of cardiac insufficiency were minimal.

Coronary Thrombosis.—In 31 cases there had been an attack of acute coronary occlusion, or there was a previous history of coronary thrombosis. It was evident that the two conditions were present at the time that the bundle branch block was first discovered. In most cases it was impossible to tell whether the bundle branch block had previously existed or whether it was a direct result of the recent coronary accident for which the patient had been brought to the hospital. It was felt that in some of these cases the two conditions might have appeared simultaneously, the thrombus being so situated as to interfere with the blood supply to the bundle branch. The total of 31 cases in this group does not include the cases in which the patients ultimately died of coronary thrombosis without having shown evidence of occlusion when the bundle branch block was discovered.

The majority of the patients were ambulatory (61.7 per cent) when the bundle branch block was first discovered, 9 per cent were partially confined to bed and 29.1 per cent were confined to bed. Many of the latter group, however, conceivably had had the lesion for some time prior to its discovery. In general, it may be said that bundle branch block does not of necessity, nor does it usually, imply that the patient will be confined to bed because of it.

PROGNOSIS

A conclusion with regard to the prognosis in bundle branch block cannot be sharply drawn. In most cases it was impossible to be certain how long the lesion had been present before it was discovered. Figures will vary depending on whether electrocardiograms are taken as a routine measure or whether they are taken only in cases of suspected heart disease. At most, one can merely determine the duration of life

after the discovery of the lesion. Notwithstanding the number of variables and extraneous factors, if a large number of patients with this lesion are studied, certain facts are revealed with regard to prognosis which may approximate the truth.

Of the 210 patients with proved bundle branch block and intraventricular block seen in a ten year period, 123 (68.8 per cent) were dead, 56 (31.2 per cent) were living and 31 could not be traced (table 3). For those who died, the average length of life after the discovery of the lesion was 0.93 years. The 56 patients who were still alive had been living for an average of 3.36 years since the discovery of bundle branch block. These figures indicate a slightly graver prognosis than that reported by previous investigators.[10] The duration of life in the

TABLE 3.—*Duration of Life in Cases of Bundle Branch Block*

	Number of Cases	Number Dead	Number Living	Number Lost	Percentage Living	Average Length of Life After Discovery of Lesion of Those Who Have Died, Yr.	Average Length of Life After Discovery of Lesion of Those Still Alive, Yr.
Group 1.....	90	58	20	12	25.6	1.11	3.35
a.....	80	54	15	11	21.7	0.97	2.90
b.....	10	4	5	1	55.5	3.00	4.70
Group 2.....	63	32	19	12	37.2	1.14	3.65
a.....	14	8	4	2	33.3	0.89	4.04
b.....	18	8	6	4	42.8	1.05	4.35
c.....	22	11	6	5	35.2	1.90	2.37
d.....	6	2	3	1	60.0	0.03	4.30
e.....	3	3	0	0	0	0.02	....
Group 3.....	7	3	2	2	40.0	0.12	0.45
Group 4.....	50	30	15	5	33.3	0.45	2.65
Total.....	210	123	56	31	31.2	0.93	3.36

cases in groups 1 and 2—typical left bundle branch block and typical right bundle branch block, respectively—was approximately the same as that reported for other series; it was slightly over 13 months for both groups.

In the cases in group 1b (the homophasic left bundle branch block of Graybiel and Sprague [4]) there was the best life expectancy for any of the groups. Of the 10 cases in this group, 4 were fatal after an average period of three years; in 5 cases the patient was living after an average period of 4.7 years. These figures are relatively so much higher than the figures for the group of cases of heterophasic type that one may be led to suspect that these curves may represent only partial bundle branch block.

The duration of life in the cases in groups 2a and 2b does not vary markedly from the averages for the entire series. Of the 22 cases in group 2c, 11 were fatal, the patient having survived for an average of

10. Willius.[1] King.[2] Wood, Jeffers and Wolferth.[3]

1.9 years after the diagnosis of bundle branch block was made. This is almost twice as long as the survival period in cases of any of the other types of right bundle branch block. In group 2d there were not enough cases for comparison with other groups. Group 2e consisted of 3 cases in which the curves were similar to those described by Wilson [7] as "electrocardiograms of an unusual type in right bundle branch block." In all 3 of our cases the patient was definitely in a terminal condition when the electrocardiogram was taken, and no previous curves had been made. These patients lived 1, 4 and 20 days, respectively. A fourth patient whose curve conformed to this pattern was seen just before death; previously there had been type 4 bundle branch block. One of Wilson's 3 patients was dead 9 days after the lesion was detected. No statement was made by Wilson with reference to the 2 other patients.

For group 4, which included cases of minor degrees of bundle block and intraventricular block, there was the worst prognosis of all. In 30 of the 50 cases death occurred after an average of 0.45 year. This is perhaps explained by the fact that in a good share of these cases the patient was in a terminal condition when admitted to the hospital. The terminal electrocardiographic picture for patients who have previously had conduction defects of various kinds shows simply a widened QRS interval and low voltage. In that respect it resembles the others in this group of cases. The inclusion of patients who were moribund tends to indicate a graver prognosis than is warranted. In 15 of the cases in group 4 the patients who are still living have survived an average of 2.65 years.

Notwithstanding the fact that for our patients with bundle branch block who have died the average duration of life has been approximately 1 year, many have lived much longer. Thirty have lived more than 4 years after the lesion was detected. Of these, 22 are still living, 2 having passed their eighth year, 6 their seventh year and 6 their sixth year.

We have made an attempt to analyze the influence of certain factors on the prognosis in cases of bundle branch block. The results are recorded in table 4. It will be noted that the factor of age does not play a constant role. In the groups of very young patients there was a higher percentage of patients still living than in the groups of older patients. For the patients from 60 to 69 years of age (the largest group) the average length of life in fatal cases was greater than that for any other age period. While it is dangerous to generalize, our figures indicate that older patients with bundle branch block do better than young patients with the same condition. Age, in and of itself, does not render the prognosis more grave.

The 3 patients with bundle branch block accompanied by a congenital cardiac lesion apparently enjoyed the best life expectancy of the entire group; however, 3 cases are not enough to permit of comparison. Patients with lesions occurring in the presence of syphilitic heart disease had a poor prognosis, while patients in whom bundle branch block was secondary to thyroid heart disease had a better life expectancy than

TABLE 4.—*Factors Influencing Prognosis in Bundle Branch Block*

All Cases	Number of Cases	Number Dead	Number Living	Living, %	Number Not Traced	Average Duration of Life After Discovery of Lesion in Those Now Dead, Yr.
All cases	210	123	55	30.8	32	0.93
Age						
0- 9	1	0	1	100.0	0	....
10-19	5	2	2	50.0	1	1.04
20-29	5	2	3	60.0	0	0.10
30-39	12	8	3	27.2	1	0.64
40-49	35	24	9	27.5	2	0.50
50-59	51	28	15	34.8	8	0.65
60-69	64	36	16	30.7	12	1.44
70-79	29	17	5	22.7	7	0.86
80-89	4	3	1	25.0	0	0.66
Etiologic factors						
Arteriosclerosis	161	94	39	29.3	28	0.91
Rheumatic fever	20	14	6	30.0	0	0.80
Syphilis	9	7	2	22.2	0	0.17
Thyroid disorder	8	3	4	57.1	1	1.77
Congenital condition	3	1	1	50.0	1	2.08
Miscellaneous conditions	5	3	0	0	2	0.00+
Sex						
Male	126	81	32	28.3	13	0.83
Female	84	42	24	36.3	18	1.08
Economic status						
Private patients	134	80	33	29.2	21	0.94
Charity patients	75	42	23	35.3	10	0.89
General condition						
Good	64	23	25	52.0	16	1.76
Fair	83	49	25	34.2	9	1.15
Poor	55	49	2	3.9	4	0.31
Cardiac enlargement	154	99	33	25.0	23	0.91
No cardiac enlargement	38	16	13	44.8	9	1.29
No previous history of heart disease	88	43	31	41.8	14	1.08
Previous history of heart disease	116	77	22	22.2	17	0.87
QRS of 0.15 sec. or longer	53	38	11	17.1	4	0.87
Delayed auriculoventricular conduction	25	20	5	20.0	0	0.83
Auricular fibrillation	29	20	6	23.0	3	0.88
Gallop rhythm	19	16	2	11.1	1	0.48
Coronary thrombosis	31	24	4	14.2	3	43.5 days

the rest of the patients. The duration of life in cases of arteriosclerotic heart disease plus bundle branch block was similar to the average duration of life in all the cases in the series. When the lesion occurred as a result of rheumatic heart disease, the duration of life was slightly less than that for the entire group.

Females tolerated the lesion better than did males. Private patients fared better than ward and dispensary patients. The general condition of the patient appeared to be an intangible factor in the prognosis.

For those whose condition was deemed poor at the time when bundle branch block was discovered, the outlook was grave, indeed, as the table shows.

The presence of other arrhythmias in association with bundle branch block indicated, in general, a lessened life expectancy. The finding of gallop rhythm, in particular, predicted an unfavorable prognosis.

For those patients who had suffered coronary thrombosis or in whom a bundle lesion was noted after acute coronary occlusion, the prognosis was poor.

Of the 123 patients who have died, 60 have died of cardiac failure, 29 of coronary thrombosis, 2 of subacute bacterial endocarditis, 2 during an Adams-Stokes attack and 26 of noncardiac conditions; in 4 cases the cause of death was not known.

Successive Electrocardiograms.—In 58 cases electrocardiograms were secured after an interval of several months to several years following the taking of the curves which first revealed the bundle branch block. In a number of instances we were able to follow the cases electrocardiographically at regular intervals over a relatively long period. In 18 cases the curves remained unchanged throughout the entire period of observation. In 16 cases they showed progression in the severity of the lesion. In 11 cases there was graphic evidence of improvement. In the remaining 13 cases there were changes which we were unable to interpret as indicating either improvement or regression. In 16 cases changes were noted in the configuration of the QRS complex of sufficient magnitude to warrant concluding that the original lesion had been altered or had been overshadowed by another one. Left bundle branch block was succeeded by right bundle branch block in a few instances and vice versa. Type 4 bundle branch block was not an uncommon terminal finding in cases of previous typical complete bundle branch block. There were also infrequent changes from one to any of the other subgroups of right bundle branch block (Bayley). Changes from one type of bundle branch block to another were frequently seen just before death: these may have been due to superimposed lesions which were the causes of death, respectively, or else they were manifestations of deranged conduction in a completely failing myocardium.

Transient Bundle Branch Block.—Herrmann and Ashman,[11] in 1931, reviewed all the previously reported cases of transient bundle branch block (10 in all) and added 8 cases of their own. Morris and McGuire [12] reported 2 cases of transient complete bundle branch block which came on acutely in association with acute circulatory failure. Hamburger [13] described a case of transient bundle branch block from digitalis in a

11. Herrmann, G., and Ashman, R.: Am. Heart J. **6**:375, 1931.
12. Morris, R. S., and McGuire, J.: Am. J. M. Sc. **184**:202, 1932.
13. Hamburger, W. W.: M. Clin. North America **13**:177, 1926.

case of advanced congestive heart failure. Willius and Anderson [14] concluded that "transient complete bundle branch block is not a rare condition." In our own series there were 9 cases of transient bundle branch block. In 4 of these cases the disorder cleared up after a course of rest in bed and digitalization, indicating that cardiac failure was probably the basis for the disturbance in conduction. However, in 3 of these cases there were recurrences of the bundle branch block during subsequent cardiac breakdowns. In 2 of the 9 cases evidence of bundle branch block developed simultaneously with the occurrence of coronary occlusion. As recovery from the coronary occlusion took place, the bundle branch block disappeared as well. In 1 case bundle branch block occurred during an attack of appendicitis and cleared up subsequent to appendectomy. In another case recovery apparently followed thyroidectomy. In the ninth case the disappearance of bundle branch block was spontaneous.

COMMENT AND SUMMARY

The entire series of electrocardiograms taken at Harper Hospital over a ten year period were reviewed. Two hundred and ten cases of bundle branch block and intraventricular block were found. In 179 cases (85.2 per cent) the subsequent course was studied; in the remainder of the cases the patient could not be followed. Using Wilson's criteria for the diagnosis of right bundle branch block, we were able to confirm his observation that that condition is more frequent than was previously supposed. The ratio of males to females in our series was 3 to 2. The largest number of cases occurred in patients in the sixth and seventh decades. About three fourths of the cases occurred in conjunction with arteriosclerotic heart disease. In 15 per cent of the cases there was evidence of frank coronary occlusion.

Patients for whom the diagnosis of bundle branch block is made come to the hospital for a variety of reasons. The diagnosis is practically never made or even suspected until disclosed by electrocardiographic evidence. Consequently, these patients first present themselves with a previous history ranging from good health to complete disability. Frequently evidence of bundle branch block is discovered in the electrocardiogram of a patient who has no other signs of cardiac disease. In such cases signs or symptoms of cardiac disease may never develop. On the other hand, our records reveal repeated electrocardiograms in cases in which bundle branch lesions suddenly developed and death occurred in a short time.

There is no "clinical picture" of bundle branch block. Although bundle branch block may be discovered in conjunction with what is to all appearances a normal or near normal heart, it is most frequently associated with some degree of cardiovascular disease. Statistics in this

14. Willius, F. A., and Anderson, M. J.: Am. Heart J. **10**:248, 1934.

regard do not show the absolute facts, because the taking of electrocardiograms is not a routine procedure and in many cases the condition is not discovered at its inception.

As electrocardiograms are usually not taken except when heart disease is suspected or when the patient's condition is being evaluated with regard to surgical or insurance risk, electrocardiographic files are somewhat overbalanced with records showing some form of cardiac damage. The records, therefore, are not a cross section of the findings for the general population or even for patients in a hospital.

In general, it may be said that bundle branch block is most frequently found in conjunction with definite heart disease aside from the bundle lesion. Consequently the prognosis in cases of bundle branch block is at best no better than it is in cases of any form of myocardial disease. How much hazard accrues from the bundle branch block is difficult to estimate. In spite of the fact that a majority of the cases occur in aged persons and in patients suffering from cardiac disease, a fair percentage of patients live for a surprising length of time and without great discomfort.

The most important factors to be considered in determining the prognosis are the general condition of the patient and the physical signs of cardiac damage. Patients who are in good condition and show little or no signs of cardiac embarrassment are not as a rule in immediate danger. Those who are suffering from other degenerative diseases and present findings of myocardial disease, such as cardiac enlargement, cardiac arrhythmia, dyspnea and peripheral edema, suffer seriously from a bundle branch lesion. Gallop rhythm is an ominous prognostic sign. In cases in which bundle branch block is associated with frank coronary thrombosis the patients are usually destined to early death.

The larger percentage of patients die within the first year after the discovery of the lesion. Those who survive this first year stand an excellent chance of carrying on for a relatively longer time.

Our patients with right bundle branch block lived slightly longer than those with a lesion on the left side. Patients with so-called intraventricular block had a poorer life expectancy than those with complete bundle branch block. Our study did not include cases in which there was a minor degree of intraventricular block.

The aged patients seemed to withstand the ill effects of bundle branch block as well as did the younger patients.

When bundle branch block was associated with syphilitic heart disease, the prognosis was poor. Patients with bundle branch block secondary to thyroid or congenital heart disease did much better than the average. The rheumatic and arteriosclerotic patients fared about equally well, the prognosis ranking between the two extremes just cited.

Females, in general, lived longer than males with this lesion. Private and charity patients showed no outstanding differences.

GASTROSCOPIC OBSERVATIONS IN PERNICIOUS ANEMIA

RUDOLF SCHINDLER, M.D.
Associate Professor of Medicine, University of Chicago
AND
A. M. SERBY, M.D.
Assistant Clinical Professor of Medicine, Rush Medical College;
Adjunct, Department of Medicine, Michael Reese Hospital
CHICAGO

The close relation between pernicious anemia and changes in the mucosa of the stomach has been well recognized since the time of Austin Flint [1] and Hayem.[2] A brilliant synopsis of all the questions involved has been given by Minot.[3] Friedenwald and Morrison [4] stated as early as 1919 that practically no patient with pernicious anemia is free from gastrointestinal symptoms.

Anatomically there was early general agreement (Faber and Bloch [5]) that the gastric mucosa was thinned or degenerated, that these changes were most pronounced in the cardiac region and that they diminished toward the pylorus. In later times this anatomic concept changed. Cases were described in which the wall of the pyloric region was tremendously thickened by inflammation of the deeper layers, especially of the muscularis propria (Kleemann [6]), and even by the formation of inflammatory polyps—gastritis hypertrophicans polyposa—in the pyloric region (Mayeda [7]). In 1934 M. R. Brown,[8] in a report on the post-

1. Flint, A.: A Clinical Lecture on Anemia, Am. M. Times **1**:181, 1860.

2. Hayem, G.: Gastrites dégénératives, Soc. méd. d. hôp., 1896, p. 722.

3. Minot, G. R.: Anemia and the Gastrointestinal Tract: A Synopsis, Am. J. Digest. Dis. & Nutrition **3**:643, 1936.

4. Friedenwald, J., and Morrison, T.: Gastro-Intestinal Disturbances in Pernicious Anemia, J. A. M. A. **73**:407 (Aug. 9) 1919.

5. Faber, K., and Bloch, C. E.: Ueber die pathologischen Veränderungen am Digestionstraktus bei der perniciösen Anämie und über die sogenannte Darmatrophie, Ztschr. f. klin. Med. **40**:98, 1900.

6. Kleemann, A.: Ueber die Hypertrophie des Pylorus bei perniciöser Anämie, Deutsche Arch. f. klin. Med. **128**:271, 1919.

7. Mayeda, T.: Ueber die Hypertrophie des Pylorus bei perniciöser Anämie, Schweiz. med. Wchnschr. **51**:699, 1921.

8. Brown, M. R.: Gastrointestinal Pathology in Pernicious Anemia and Subacute Combined Degeneration of the Spinal Cord, New England J. Med. **210**: 473, 1934.

mortem examinations in 151 proved cases of pernicious anemia, emphasized the frequency of all kinds of gross gastric lesions, not only atrophic gastritis but also benign inflammatory polyps and carcinoma. The gastritis he regularly observed was not only of the atrophic type but also partly of the hypertrophic type. However, he stated that the apparent hypertrophy consisted of interstitial infiltration with leukocytes and replacement of the tubules by fibrous tissue. This description does not agree with the modern definition of hypertrophic gastritis, i. e., not destruction but definite proliferation of tubules accompanied by interstitial infiltration. At any rate, he noted a marked inflammatory process, not merely a degenerative or regressive process. Furthermore, Brown discovered that in 20 cases in which liver therapy had been received no decisive influence was apparent in the histologic picture. Still more important was his observation that the gastritis was most severe near the pylorus. Most of the polyps observed occurred in this region. He also observed enteritis often. These observations seemed to fit in with the theory that inflammatory changes in the pyloric mucosa and the duodenum were the primary cause of pernicious anemia. The so-called pyloric organ, consisting of the Brunner glands of the antrum and the duodenum, is believed to secrete, to a large extent, the "intrinsic factor" (Castle [9]) the absence of which is apparently necessary to cause the entity of pernicious anemia. These observations of Brown therefore agreed closely with the ideas of Faber [10] and Hurst [11] on the importance of primary inflammation of the stomach in the origin of this disease.

It is natural that attempts were made to observe the living gastric mucosa in patients with pernicious anemia by means of the safe flexible gastroscope, which by that time had been invented.[12] This method seemed especially important, since after the routine administration of

9. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: I. Effect of the Administration to Patients with Pernicious Anemia of the Contents of a Normal Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. M. Sc. **178**:748, 1929. Castle, W. B., and Townsend, W. C.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: II. Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, ibid. **178**:764, 1929. Castle, W. B.; Townsend, W. C., and Heath, C. W.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, ibid. **180**:305, 1930.

10. Faber, K.: Gastrititis and Its Consequences, New York, Oxford University Press, 1935.

11. Hurst, A. F.: The Unity of Gastric Disorders, Brit. M. J. **2**:89, 1933.

12. Schindler, R.: Gastroscopy: The Endoscopic Study of Gastric Pathology, Chicago, University of Chicago Press, 1937.

liver therapy (Whipple [13]) autopsy material became rare. Henning,[14] on the basis of his great experience in this field, contended that in each patient with pernicious anemia, diffuse atrophy of the entire gastric mucosa could be observed. Gutzeit and Teitge [15] detected atrophic changes in every patient and said they believed that they never disappeared, in spite of liver therapy; although Teitge observed alterations of pictures, which he said he considered to be due to acute inflammatory attacks. Lehmann,[16] in a monograph published in 1936, reported on 3 cases of pernicious anemia. In the first case he observed in the pale mucosa patches of atrophic gastritis which disappeared almost completely after treatment; the blood vessels that were demonstrable at the first examination disappeared; four small gray patches were the residuum of the foregoing severe atrophic gastritis. The second patient was observed with the gastroscope during a complete remission; only one atrophic patch was seen on the anterior wall. In the third patient, observed during an incomplete remission, only slight diffuse atrophy was seen. In the first 2 cases the improvement of the "tongue of Hunter" equaled that of the changes in the gastric mucosa. Similar cases have been described by René Chevallier.[17]

The most important observations were made on 5 patients by Jones, Benedict and Hampton.[18] Their paper presented observations made during remissions and in 3 of these patients also during relapses. In their first patient carcinoma developed. The second patient was studied because of the formation of polyps during a remission, and hypertrophic gastritis was noted; later, however, the mucosa appeared normal gastroscopically. The third patient presented in relapse an atrophic mucosa, which later showed hypertrophic gastritis. The fourth patient was operated on in a remission, and the mucosa appeared red and inflamed and was covered with small "polyps." Four years later the mucosa was practically normal. In the fifth patient they saw that during relapse the mucosa was atrophic and that during a remission it was normal. The authors stated that in each instance no atrophy was present after

13. Whipple, G. H., and Robscheit-Robbins, F. S.: Blood Regeneration in Severe Anemia: Standard Basal Ration Bread and Experimental Methods, Am. J. Physiol. **72**:395, 1925.

14. Henning, N.: Die Entzündung des Magens, Leipzig, Johann Ambrosius Barth, 1934.

15. Gutzeit, K., and Teitge, H.: Die Gastroskopie, Berlin, Urban & Schwarzenberg, 1937.

16. Lehmann, R.: Les atrophies gastriques dans les anémies idiopathiques et les métanémies, Paris, E. Le François, 1936.

17. Chevallier, R.: Intérêt de la gastroscopie dans les anémies graves, Lyon méd. **158**:61, 1936.

18. Jones, C. M.; Benedict, E. B., and Hampton, A. O.: Variations in Gastric Mucosa in Pernicious Anemia, Am. J. M. Sc. **190**:596, 1935.

successful treatment and that hypertrophic changes also subsided. They suggested, however, that the change from atrophy to normal represents epithelial changes associated with successful treatment of a specific deficiency state rather than the healing of a chronic inflammatory process, while the apparent return to normal from a grossly hypertrophic condition of the gastric mucous membrane represents subsidence of chronic gastritis. We shall reconsider these conceptions in our own conclusions. Evidently these authors were the first directly to observe the complete healing of atrophy of the gastric mucosa as a result of liver therapy.

Since there were so many points of disagreement among the observers using the gastroscope, we decided to compile the data for all our cases of pernicious anemia in which there was no doubt about the diagnosis, considering especially the following questions: 1. What is the nature of the changes in untreated patients? 2. How does the gastric mucosa appear after sufficient therapy? Does the aspect of the mucosa change during therapy? Can it become normal? 3. What is the usual site of the gastric lesions? 4. Is it possible to make some statements concerning such complications as hypertrophic gastritis, the formation of polyps or carcinoma? 5. Do the gastroscopic observations contribute to the theory of the origin of pernicious anemia?

No autopsy material was available. In the 1 case in which death occurred (case 6), necropsy could not be performed. Only such definite changes as are never seen in healthy persons were recorded as abnormal. In almost all instances the so-called 50 degree Wolf-Schindler gastroscope, which has a greater resolving power than the usual 80 degree instrument, was used. All cases in which the diagnosis was uncertain were discarded.

This paper, then, is based on the gastroscopic observation of 23 patients suffering undoubtedly from pernicious anemia.[19] Five of these patients were examined with the gastroscope repeatedly (2 of them twice, 2 of them three times and 1 of them six times), so that a total of thirty-four gastroscopic examinations were carried out on the 23 patients. In order to abbreviate the case reports it is mentioned that all the patients offered a cleancut picture of pernicious anemia, that most of them had some, though often slight, gastric distress and that combined degeneration of the spinal cord of varying degree was often present.

Six of the 23 patients did not receive adequate treatment. Fourteen of these 23 patients were observed only after sufficient or almost suffi-

19. Ten of these patients were referred by Dr. E. Kandel, head of the hematologic department of the University of Chicago; 1 was referred by Dr. W. L. Palmer, head of the gastrointestinal department at Billings Hospital; 3 were patients of Dr. C. Eiseman, of the Oak Forest (Ill.) Hospital; 8 were examined at Michael Reese Hospital, and 1 was observed with Dr. Leon Schiff at the Cincinnati General Hospital.

cient treatment. Three of the 23 patients were observed first before treatment and then again after sufficient or almost sufficient treatment. An additional patient was studied (case 24) in whom pernicious anemia was not found but who had atrophic gastritis which responded to liver therapy. This case history seems to be important in connection with the theoretic discussion.

The gastroscopic features of the gastric mucosa have been described so thoroughly elsewhere [20] that extensive repetition would be superfluous.

REPORT OF CASES

A. Patients observed gastroscopically who had not had treatment.

CASE 1.—A 72 year old man entered the Oak Forest (Ill.) Hospital because of weakness, edema of the feet and peculiar sensations in the fingers and toes for about two years. Examination revealed typical pernicious anemia. The blood count made at the time of the gastroscopic examination showed: hemoglobin, 35 per cent, and erythrocytes, 1,950,000.[21]

Gastroscopic Examination.—The antrum and the body of the stomach presented throughout an atrophic mucosa. A few pinkish islands and ridges were observed in the anterior and posterior wall of the body. The diagnosis was diffuse atrophy of the entire gastric mucosa.

CASE 2.—A woman aged 69 was seen at Billings Hospital. For two months she had had excessive weakness and fatigue, cramplike pains below the knees, bloating, gaseous belching that was not connected with meals, and rarely nausea and vomiting. The clinical features were typical of pernicious anemia. The hemoglobin value was 65 per cent, and the erythrocyte count was 1,720,000.

Gastroscopic Examination.—The pylorus contracted energetically, with a mushroom-like protrusion. The mucosa of the antrum was definitely gray and thin. The musculus sphincter antri was smooth. The entire mucosa, increasingly toward the cardia, was thin and gray and contained many thick branching blue and red blood vessels. The diagnosis was complete atrophy of the gastric mucosa.

Comment.—The picture in these 2 cases evidently corresponds with that seen by Henning and Gutzeit. It is the classic picture of a thin, smooth, gray completely atrophic mucosa, as described by Hayem.

CASE 3.—A 54 year old woman was seen at Billings Hospital. She complained of severe belching, rumbling and gurgling in the abdomen, tingling of the fingers and toes and general malaise. The physical examination revealed the typical picture of pernicious anemia plus combined degeneration of the spinal cord. The hemoglobin value was 60 per cent and the red blood cell count 2,670,000.

Gastroscopic Examination.—A gastroscopic examination was made, and the diagnosis was complete atrophy of the mucosa of the antrum and patchy atrophic hemorrhagic gastritis of the mucosa of the body of the stomach.

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20. (*a*) Schindler, R.; Ortmayer, M., and Renshaw, J. F.: Chronic Gastritis, J. A. M. A. **108**:465 (Feb. 6) 1937. (*b*) Schindler.[12]

21. The white blood cell count and the blood smear will not be reported on. The latter in cases in which treatment had not been received always was characteristic of pernicious anemia.

Comment.—In this case the antrum was decidedly more atrophic than the body. If one were to observe many similar conditions one would be inclined to agree with Faber's theory that primary inflammation of the pyloric organ is the primary cause of pernicious anemia. The following cases show, however, that this location of mucosal changes is an exception rather than the rule.

CASE 4.—A 58 year old woman was admitted to Billings Hospital. She complained of loss of weight, loss of appetite, weakness and soreness of the mouth and tongue. Hers was a typical case of pernicious anemia, without changes in the spinal cord. The hemoglobin value was 60 per cent and the red blood cell count 2,460,000.

Gastroscopic Examination.—A gastroscopic examination was made, and the diagnosis was circumscribed patchy atrophic gastritis of the lower portions of the body of the stomach.

Comment.—This case proves that there are cases of untreated pernicious anemia in which gross atrophic changes are not seen in the antral mucosa but only patchy atrophy is seen in the mucosa of the body. On the other hand, these patches were not situated close to the cardia but in the distal portions of the body of the stomach.

CASE 5.—Dr. Leon Schiff permitted us to study this patient at the Cincinnati General Hospital. The clinical findings were those of severe untreated pernicious anemia.

Gastroscopic Examination.—The pylorus and the antrum were normal. The mucosa of the lower portions of the anterior wall looked slightly granular and thin. Grayish patches were seen in the orange-red mucosa. The upper portion of the stomach was completely atrophic and greenish gray, with two sets of branching blood vessels in the posterior wall.

Comment.—In this case the most marked atrophic changes were seen close to the cardia; they became less in the lower portions of the body and were absent in the antrum.

CASE 6.—A 70 year old woman was seen at the Oak Forest (Ill.) Hospital. She had untreated pernicious anemia. Death occurred, but permission for autopsy was not given. The clinical picture was typical of pernicious anemia. The time of the onset of the disease was unknown. The hemoglobin value was 53 per cent and the red blood cell count 2,750,000.

Gastroscopic Examination.—The first gastroscopic examination was made on Nov. 30, 1936. There were extensive superficial gastritis of the whole stomach (antrum and body); pallor of the mucosa and multiple polyps but no atrophy. The second examination, made on May 13, 1937, showed slight atrophy of the anterior wall of the body, marked superficial gastritis of its upper portion, polyps of the antrum and of the lower portion of the body and a normal mucosa in the antrum.

Comment.—This case seems to be especially important. The clinical picture was typical of pernicious anemia, and the patient later died of this disease. At the first gastroscopic examination, no sign of atrophy was

discovered, but marked superficial inflammation of all portions of the gastric mucosa was noted. Later, this superficial inflammation was seen only in the upper portions of the body, while some portions of the mucosa of the body had become definitely atrophic. The mucosa of the antrum, however, had become normal, although no treatment had been given. This observation proves that there are cases of pernicious anemia in which superficial gastritis is present without any visible atrophy and that atrophy following this superficial inflammation can occur at a later stage. One may argue that the superficial epithelial cells might already have been changed by some regressive process, which then facilitated infection and subsequent severe inflammation. This, however, is hypothetic, and it would be impossible to prove or to contradict such a conception. It is certain that atrophy of the mucosa itself—thinning and graying—was not present, although pernicious anemia was marked and advanced. Furthermore, definite atrophy developed later, while superficial gastritis was found only in the upper portions of the mucosa of the body. Finally, the superficial gastritis of the antrum subsided without changing into atrophy. We are inclined to consider this case as proof that the atrophy, both the patchy and the diffuse form, seen in patients with pernicious anemia is inflammatory rather than purely regressive. It is interesting that the superficial gastritis led to atrophic gastritis only in the body, whereas the antrum became normal. The frequency of benign tumors in cases of pernicious anemia is well known. It is remarkable that in this case benign polyps were found in an inflamed but not atrophic mucous membrane.

B. Patients observed gastroscopically after having had liver therapy.

CASE 7.—A 54 year old man was admitted to Michael Reese Hospital. For one year he had complained of headache, weakness, pains in the legs and loss of weight. He was pale, and the tongue was atrophic. The complete picture of pernicious anemia was found, the hemoglobin value being 60 per cent and the red blood cell count 1,780,000. After systematic treatment with liver the hemoglobin value was 80 per cent and the red blood cell count 4,440,000. The tongue had become normal. The patient's general condition was good.

Gastroscopic Examination.—The gastroscopic examination revealed extensive patchy atrophic gastritis of the antrum and lower parts of the body of the stomach.

Comment.—In this case, in which marked atrophic changes similar to those in untreated patients were present, it is impossible to decide whether the condition of the gastric mucosa had improved as a result of treatment. That the treatment had been rather satisfactory was proved not only by the hematologic findings but also by the return of the tongue to normal. Evidently in this case there was no parallel between the condition of the tongue and that of the gastric mucosa.[22]

22. Chevallier, P., and Moutier, F.: Langue et estomac, Presse méd. **43**:1801, 1935.

CASE 8.—A 58 year old patient was admitted to Michael Reese Hospital, complaining of weakness, numbness and tingling in the extremities, dyspnea, edema, nausea and loss of weight for one year. Before treatment the tongue was smooth, no free hydrochloric acid was found in the stomach contents, the hemoglobin value was 27 per cent and the red blood cell count was 1,000,000.

Gastroscopic Examination.—At the time of the gastroscopic examination the hemoglobin value was 85 per cent and the red blood cell count 4,790,000. The gastroscopic diagnosis was extensive diffuse atrophic gastritis of the whole stomach.

Comment.—In this case the treatment had been sufficient, yet all portions of the stomach showed marked atrophic gastritis.

CASE 9.—A 56 year old woman was admitted to Michael Reese Hospital. She had had burning epigastric sensations for eighteen months. Dyspnea developed, and the gastric pain became severe. She became weak and tired easily and had nausea and vomiting. Physical examination showed the typical picture of pernicious anemia. After liver treatment the hemoglobin value rose from 35 to 75 per cent and the red blood cell count from 1,400,000 to 4,120,000.

Gastroscopic Examination.—At the time of the gastroscopic examination she complained of only slight gastric pain. The diagnosis was diffuse, almost complete atrophic gastritis of the whole stomach.

Comment.—It may be that in this case the treatment had not been sufficiently energetic. It is noteworthy that the subjective condition and the blood picture made such great strides forward while the gastric mucosa remained so completely atrophic that improvement as a result of therapy could scarcely be assumed.

CASE 10.—A 32 year old man had been treated for pernicious anemia for seven years (1930 to 1937). At the time of gastroscopic examination at Billings Hospital he felt fine. With liver therapy the hemoglobin value had increased from 30 to 90 per cent and the red blood cell count from 1,370,000 to 5,700,000.

Gastroscopic Examination.—The gastroscopic diagnosis was extensive, almost complete atrophic gastritis of the antrum and the body.

Comment.—In this case the therapy had been sufficient. The blood picture was normal, and the patient felt fine; nevertheless, the gastric mucosa showed almost complete diffuse atrophic gastritis.

In the following 5 cases the mucosal changes were less marked:

CASE 11.—A 47 year old woman was seen at Michael Reese Hospital. She had suffered from anorexia, weakness and dizziness for six years. Typical pernicious anemia was detected, and liver therapy was given. At the time of gastroscopic examination, the condition had much improved: the hemoglobin value was 80 per cent and the red blood cell count 4,300,000.

Gastroscopic Examination.—In the greater curvature of the antrum a small, reddened prominence (polyp) was seen. In the lesser curvature of the body some parallel folds were present. The valleys between them presented a thinned, grayish mucosa. All other portions of the body had a normal appearance. The diagnosis was slight patchy atrophic gastritis of the lesser curvature of the body. There was a small polyp in the antrum.

Comment.—This result of sufficient liver therapy corresponds well with the results obtained by P. Chevallier and Moutier and by Lehmann.

CASE 12.—A 35 year old man was seen at Michael Reese Hospital. He complained of exhaustion, loss of weight, anorexia, abdominal pressure and soreness of the tongue for four months. The physical examination revealed the complete picture of pernicious anemia. The tongue was atrophic; anacidity was demonstrated by the histamine test. The hemoglobin value was 45 per cent and the red blood cell count 1,150,000. Injections of liver extract were given and the condition improved considerably.

Gastroscopic Examination.—At the time of the gastroscopic examination the hemoglobin value was 72 per cent and the red blood call count 4,300,000. The gastroscopic diagnosis was patchy atrophic gastritis of the body only. The antrum was normal.

Comment.—In this case also the extensive atrophic patches were found only in the body of the stomach.

CASE 13.—A 72 year old man was admitted to Billings Hospital. He complained of loss of weight, swelling of the ankles, numbness and tingling in the hands and feet, difficulty in walking, and itching. The diagnosis was pernicious anemia with combined degeneration of the spinal cord. He had had some liver treatment for one year before entry, so that the original figures for the hemoglobin and red blood cells were not available. However, the blood count was about normal: hemoglobin, 99 per cent, and red blood cells, 4,560,000.

Gastroscopic Examination.—The gastroscopic diagnosis was slight patchy atrophic gastritis of only the distal portions of the stomach. There was one small mucosal hemorrhage.

Comment.—In this case the typical changes were almost completely absent. However, remainders were observed in the antrum and in the lower portions of the stomach.

CASE 14.—A 61 year old patient was admitted to Billings Hospital. He had been treated for three years for pernicious anemia and combined degeneration of the spinal cord. In the beginning the hemoglobin value was 50 per cent and the red blood cell count 2,480,000. After injections of liver extract the blood had become normal. Before the gastroscopic examination the hemoglobin value was 103 per cent and the red blood cell count 4,900,000.

Gastroscopic Examination.—The gastroscopic diagnosis was extensive, patchy atrophic gastritis of only the anterior wall of the body.

Comment.—In this case the blood picture was completely normal. Nevertheless, extensive atrophic changes were observed, but only in the anterior wall of the body; the antrum was normal.

CASE 15.—A 49 year old man was seen at Billings Hospital. One year previously, pernicious anemia had been discovered. His complaints were of weakness and sore throat. At that time the red blood cell count was as low as 2,000,000. A histamine test showed anacidity. After injections of liver extract for five years the blood picture became normal and remained so.

Gastroscopic Examination.—At the time of the gastroscopic examination the hemoglobin value was 98 per cent and the red blood cell count 4,650,000. Gastroscopic examination revealed that the mucous membrane, especially in the upper portions, was thinner than normal, with gray spots and small blood vessels. These changes were not striking.

Comment.—This patient had been well treated for pernicious anemia and showed a normal blood picture. However, there was slight but definite patchy atrophiic gastritis in the upper portion of the stomach.

Case 16.—A 51 year old patient was admitted to Michael Reese Hospital. He had been examined seven years previously, and at that time the typical picture of pernicious anemia was found. The hemoglobin value was 60 per cent and the red blood cell count 2,700,000. He then received liver therapy regularly. Signs of degeneration of the spinal cord were found later. The administration of liver had lately been rather irregular. The blood picture, however, was satisfactory.

Gastroscopic Examination.—At the time of the gastroscopic examination the hemoglobin value was 90 per cent and the red blood cell count 4,430,000. The gastroscopic diagnosis was as follows: slight patchy atrophic gastritis of the anterior wall and marked superficial gastritis of the fornix.

Comment.—It will be noted that in all the 6 patients who received sufficient or almost sufficient treatment and who showed only patchy atrophic areas at gastroscopic examination, these patches were located in the body, the antrum being free. The only exception was case 13, in which the antrum also was involved. It should be borne in mind, however, that exclusive involvement of the antrum may occur in cases of untreated pernicious anemia (cases 4 and 5). In the last described case (case 16) superficial gastritis of the fornix was seen. In order to avoid misinterpretation one should be aware that superficial gastritis can be found alone and preceding atrophy in cases of untreated pernicious anemia (case 6). It is not likely that this finding was caused by the treatment in this case.

Case 17.—A 74 year old man was examined gastroscopically six times at Michael Reese Hospital. He was first seen two years before the first gastroscopic study. At that time he complained of weakness, loss of weight, epigastric distress and nausea. The physical examination revealed pallor, an atrophic tongue and absence of free hydrochloric acid with the histamine test. The blood picture was that of pernicious anemia, the hemoglobin value being 52 per cent and the red blood cell count 2,690,000. After liver treatment the blood findings were as follows:

Gastroscopic Study	Hemoglobin, %	Red Blood Cell Count, Thousands
1	75	4,140
2	82	4,140
3	77	4,350
4	69	4,110
5	60	4,280
6	70	4,180

Gastroscopic Examination.—The six gastroscopic studies were carried out within one year (November 1936 to October 1937), and the following reports were made:

Nov. 12, 1936: The entire stomach was seen. The mucosa of the antrum was normal but contained three prominent hemispheric "stalagmite" polyps. The mucosa of the body was covered with small amounts of adherent mucus but was not atrophic. In the middle of the body, in its posterior wall toward the greater curvature, another polyp was seen. It had a broad base and was dark red and somewhat ulcerated. A fifth polyp with a broad base was seen beneath the cardia. At this time definite superficial gastritis without atrophy was seen.

Jan. 15, 1937: At this examination additional polyps were observed. The pyloric action was normal. In the antrum six polyps were seen. A seventh was in the posterior wall of the midportion of the stomach. It was dark red and contained many yellow ulcerations. The eighth was high up on the posterior wall, about 4 cm. below the cardia. It had a broad base and was reddened and partly ulcerated. All other portions of the mucous membrane were normal. At this examination the superficial gastritis had disappeared. No atrophy was observed. The mucosa was not pale. The number of polyps had increased. The appearance of two of them was highly suggestive of beginning malignant growth.

Feb. 16, 1937: The mucous membrane was normal. Most of the polyps were unchanged. However, the seventh one apparently had grown. Its surface was irregular and nodular and was covered with whitish mucus. The eighth (highest) polyp had not grown but had such an irregular shape that without the other appearance of polyposis we would have made a diagnosis of beginning carcinoma.

April 16, 1937: At this examination only the upper polyps were well visualized. The mucous membrane looked normal.

May 20, 1937: The color of the mucus membrane appeared normal; the mucosal folds were normal. The appearance of the polyps had not changed.

Oct. 1, 1937: There was marked superficial antral gastritis.

Comment.—This patient may not have been treated sufficiently. Nevertheless, at none of the six gastroscopic examinations was any sign of atrophy discovered. Twice, however, at the first and at the sixth examination, definite superficial gastritis was seen. Without the knowledge of the condition in untreated pernicious anemia (case 6) we would have considered that these periods of superficial gastritis were due in some way to the treatment. That case has taught us that the same picture may be found without any treatment. Eight polyps were present. Malignant degeneration was not observed, although two of the tumors were highly suggestive of beginning malignant growth. In almost every case of benign tumor of the gastric mucosa, accompanying atrophic gastritis is found gastroscopically. Therefore, it must be assumed that the absence of atrophic changes in this case was due to the liver therapy.

In the 3 following cases no pathologic changes were seen after successful treatment.

CASE 18.—A 36 year old woman was admitted to Billings Hospital. She was seen first in 1933, when she complained of dizzy spells, indigestion and extreme nervousness. The blood picture showed the characteristics of pernicious anemia. The hemoglobin value was 57 per cent and the red blood cell count 1,990,000.

No free hydrochloric acid was found. She recovered after receiving liver therapy. In 1935 the hemoglobin value was 106 per cent and the red blood cell count 5,480,000.

Gastroscopic Examination.—Gastroscopic examination showed that the stomach was normal.

Comment.—In this case there was slight polycythemia after treatment for severe pernicious anemia. The gastric mucosa was normal.

CASE 19.—A man aged 38 had entered Billings Hospital in 1933 and had been under treatment in the hematologic department since then. His chief complaint was of weakness. He had slight evidence of degeneration of the spinal cord, there was no free hydrochloric acid in the gastric contents and the blood picture was typical of pernicious anemia, the hemoglobin value being 60 per cent and the red blood cell count 2,540,000.

Gastroscopic Examination.—Gastroscopic examination revealed that the stomach was normal.

CASE 20.—A 58 year old woman was admitted to Billings Hospital in 1932 and was under observation until 1936. Her chief complaints in the beginning were of weakness, numbness of the extremities and severe headache. A diagnosis of pernicious anemia with mild combined degeneration of the spinal cord was made. No free hydrochloric acid was found. The hemoglobin value was 51 per cent and the red blood cell count 2,080,000. After liver therapy and at the time of the gastroscopic examination the blood count showed: hemoglobin, 95 per cent, and red blood cells, 4,220,000.

Gastroscopic Examination.—Gastroscopic examination revealed that the stomach was normal.

Comment.—While the patients in cases 18 and 19 perhaps were somewhat "overtreated," the blood count in case 20 was normal, and normal gastric mucosa was found gastroscopically. One should compare this case with cases 7, 8 and 10, in which the blood picture had become entirely normal but the gastric mucosa was still almost completely atrophic. Only the findings in cases 18, 19 and 20 agree with those presented by Jones, Benedict and Hampton.[18]

C. Patients observed gastroscopically before and after liver therapy.

CASE 21.—A man aged 70 was admitted to Oak Forest (Ill.) Hospital. He was first seen immediately before the gastroscopic examination. He was completely deaf. He was anemic and had edema of the legs and signs of combined degeneration of the spinal cord. No free hydrochloric acid was found in the gastric contents. The hemoglobin value was 37 per cent and the red blood cell count 1,280,000. The blood smear showed changes typical of pernicious anemia.

Gastroscopic Examination.—On Nov. 28, 1936, examination revealed extensive atrophic gastritis of the whole stomach.

The patient was then given liver therapy. Either the dosage was not adequate, or the patient did not react to liver. Half a year later the hemoglobin value was 73 per cent and the red blood cell count 3,710,000. The smear still showed achromia and anisocytosis. However, the gastroscopic picture had changed entirely. On May 13, 1937, examination showed marked regression of the atrophic gastritis. There was slight atrophic hemorrhagic gastritis of the highest portion of the lesser curvature.

Comment.—In this case regeneration of a previously atrophic mucous membrane could be followed in its stages by repeated gastroscopic examination. The end result of this regeneration had been observed in cases 18, 19 and 20. The blood picture returned almost to normal. The mucous membrane of the distal portions of the stomach appeared to be normal, and only the upper portion of the lesser curvature showed atrophic hemorrhagic inflammation. In cases 18 to 21 the mucous membrane was definitely normal; there was none of the overlapping, thickening or inflammation described by Gutzeit and Teitge.[15] A real regeneration had taken place.

Still more impressive was the following case.

CASE 22.—A 53 year old woman was admitted to Michael Reese Hospital. She was first seen in 1934, when she said she had had progressive weakness for two years, uncomfortable fulness after meals, nausea and vomiting. Pernicious anemia was diagnosed because of the characteristic blood picture, i. e., a hemoglobin value of 45 per cent and a red blood cell count of 1,410,000. After liver therapy her condition improved considerably (hemoglobin value, 80 per cent; red blood cell count, 4,400,000). Between June and October 1936 she voluntarily stopped treatment, and consequently the hemoglobin value dropped to 45 per cent and the red blood cell count to 2,050,000.

Gastroscopic Examination.—Examination on Nov. 5, 1936, showed: pallor of the mucosa, atrophic gastritis of the antrum and of the upper portions of the body, and some small mucosal hemorrhages.

The distribution of the atrophic changes at this observation is noteworthy. The antrum and the upper portions of the body were atrophic; and the lower portion of the body, usually the seat of the most outspoken change, was normal.

The next gastroscopic examination was carried out about one month later, after liver therapy. The hemoglobin value then was 72 per cent and the red blood cell count 3,560,000. An almost normal blood picture had been attained.

A second gastroscopic examination, on Dec. 7, 1936, showed disappearance of pallor, disappearance of atrophic gastritis of the antrum, atrophic gastritis of the upper portions of the body and one mucosal hemorrhage in the posterior wall.

About two months later the blood picture was normal, the hemoglobin value being 90 per cent and the red blood cell count 4,940,00. In this short time the gastroscopic picture had changed entirely. A third gastroscopic examination, on Feb. 11, 1937, showed that the stomach was normal.

Comment.—In this case the changes in the gastric mucosa as a result of liver therapy were observed at three gastroscopic examinations. At first the antrum was atrophic, and the upper portions of the body presented marked patchy atrophic gastritis. After one month of treatment the antral mucosa had become normal, whereas the mucosa of the body still presented definite atrophic gastritis. After three months of treatment, complete regeneration had taken place.

CASE 23.—A 61 year old patient was admitted to Billings Hospital. The chief complaints were of difficulty in walking and numbness of the hands and legs. The findings were typical of pernicious anemia with combined degeneration of the

spinal cord. At the time of the first gastroscopic examination the hemoglobin value was 75 per cent and the red blood cell count 2,720,000. No free hydrochloric acid was found.

Gastroscopic Examination.—At the first gastroscopic examination, on April 3, 1935, two patches of atrophic gastritis in the lower portion of the body and in the fornix were observed.

Eighteen days later, after liver therapy, the hemoglobin value was 82 per cent and the red blood cell count 3,300,000.

A second gastroscopic study was made, on May 14, 1935. The body of the stomach presented exactly the same picture as at the previous examination; i. e., there were two atrophic areas. In the antrum were some stiff folds.

After continued liver therapy the hemoglobin value rose, within an additional two months, to 99 per cent and the red blood cell count to 4,620,000.

A third gastroscopic examination on July 23, 1935, revealed complete atrophy of the upper portions of the body and marked hypertrophic gastritis of the greater curvature of the antrum.

Comment.—The findings in this case are different from those in all the others. Before the beginning of any therapy only two atrophic patches in the body of the stomach were seen. After the blood picture had become normal, with adequate therapy, it was found that the atrophic areas had increased in size considerably; at the same time hypertrophic changes had developed in the antrum. The occurrence of hypertrophic gastritis in this case may perhaps be explained by some kind of overcompensation by the mucosa. But there is no explanation as to why such compensation was not found in any of the other 21 cases. Another important point is the progression of the atrophic changes, in spite of liver therapy. This will be discussed later. It is easy to understand that anatomic degenerative changes caused by a deficiency status may become stationary and even irreversible after the disappearance of the deficiency status. It is impossible for us to understand why such degenerative changes should continue after the elimination of the deficiency status, if we are not willing to assume that they are effected, at least partly, by chronic progressive inflammation. This is proved especially by case 10.

D. A patient with chronic atrophic gastritis which responded to liver therapy.

This patient does not properly belong to our group of patients with pernicious anemia. The case will be discussed briefly because it appears to be essential with reference to the theoretic questions arising from the observations of other authors and from our own observations. P. Chevallier observed patients suffering from unexplainable fatigue and abdominal distress in whom atrophic gastritis was found gastroscopically and for whom liver therapy gave the most gratifying results. He perceived here, correctly, a definite relation to the classic picture of hyperchromic anemia. He therefore chose the term anemia without anemia,

or metanemia, to designate this clinical picture. In our opinion this nomenclature is not accurate. It is misleading to call a disease anemia, even with the prefix meta, if no anemia is present. Furthermore, the most important feature of real pernicious anemia is missing in these cases, namely, the malignant character, with the fatal course. We desire to be careful in evaluating these cases and deem it better to call them cases of chronic atrophic gastritis caused by a deficiency state. We feel sure that this category later must be split up. There are probably many cases in which atrophic gastritis is caused by a deficiency state without any relation to that found in pernicious anemia. Here these cases will not be considered. If, however, a patient with atrophic gastritis responds to liver treatment, then a certain if even remote relation to pernicious anemia scarcely can be denied. Therefore, we shall discuss the following case:

Case 24.—A 49 year old woman was seen at Billings Hospital. Since 1932 she had been treated for "chronic functional colitis." Her chief complaints were of epigastric pains, chronic constipation, severe generalized headache, dizziness and vomiting. For several years she also had had numbness of the feet and hands and some vague soreness of the mouth and tongue. Hunger pains were observed, sodium bicarbonate giving some relief. She complained of belching and bloating. For five years she had been taking cathartics. After defecation she felt relieved. Her appetite was fairly good. She had considerable chronic fatigue and nervousness.

The physical examination was essentially unimportant. A histamine test showed anacidity. The blood picture was normal, the hemoglobin value being 80 per cent and the red blood cell count 4,550,000. The blood smear did not show any abnormality.

The patient was followed for three years, and no definite improvement occurred. A careful examination of the nervous system did not reveal definite evidence of combined degeneration of the spinal cord. Repeated histamine tests confirmed the absence of free hydrochloric acid. No pathologic condition was revealed roentgenographically.

Gastroscopic Examination.—The first gastroscopic study was made on July 12, 1935. It revealed marked atrophic gastritis of the body of the stomach. At that time the hemoglobin value was 82 per cent and the red blood cell count 4,680,000. A second gastroscopic study was carried out, on March 24, 1936. At that time the hemoglobin value was 85 per cent and the red blood cell count 4,900,000. There was marked atrophic hemorrhagic gastritis of the entire body of the stomach. In other words, the mucosa of the stomach offered essentially the same aspect that it had nine months before. After this observation, injections of liver extract were given regularly. After about three months of this treatment the patient felt much better. Most of her distress had disappeared. The blood picture was unchanged, but a third gastroscopic examination, carried out on June 15, 1936, showed an entirely different condition. The stomach was normal. Regeneration of the previously atrophic mucous membrane had followed the institution of liver therapy.

This regeneration of a previously atrophic mucosa following liver therapy naturally was considered to be an amazing event. Liver treatment was continued

for several months. However, when we examined the patient the fourth time, on Oct. 28, 1936, we did not know that she had discontinued the therapy for more than four weeks and were surprised to find a marked relapse. The blood count at that time showed a hemoglobin value of 71 per cent and a red blood cell count of 4,900,000. Gastroscopic examination revealed patchy atrophic hemorrhagic gastritis of the body, which was less marked than at the first gastroscopic examination.

Comment.—In this case the cessation of liver therapy for several weeks had sufficed to cause a marked relapse. It must be emphasized that we have observed several patients with diffuse atrophic gastritis without hematologic changes on whom liver therapy had no effect at all. It is impossible to decide whether simple inflammation, perhaps a sequel to superficial gastritis, had been present or whether a deficiency state had also been present, the deficiency being different from that found in pernicious anemia (as for instance, lack of iron or vitamin A or B).

COMMENT

The peculiarities of the cases described have already been briefly discussed. The findings may be summarized as follows:

1. *Kind and Site of the Gastric Lesions.*—In 9 cases of untreated pernicious anemia (cases 1 to 6 and 21 to 23) no case was found in which the gastric mucosa was normal. In 8 of these cases the typical signs of atrophic gastritis were observed. The well known picture of atrophy of the entire mucosa (of the body as well as of the antrum) was observed in only 3 cases (cases 1, 2 and 21). In 2 cases (cases 3 and 22) patchy gastritis of both the antrum and the body was observed; in case 3 the antrum most decidedly was more affected than the body. In 3 cases (cases 4, 5 and 23) the antrum was normal, but marked patchy atrophic gastritis was found in the body.

In 1 case (case 6) the findings were peculiar and of great interest theoretically. At the first examination, extensive superficial gastritis of the entire stomach was seen. At the second examination some patches of atrophy had developed in the body, superficial gastritis was still present in the fornix and the antrum had become entirely normal; nevertheless, the patient died a short time later of untreated pernicious anemia.

Seventeen patients were observed gastroscopically after having had adequate or almost adequate treatment (cases 7 to 23). Three of them had been examined with the gastroscope before treatment. In 4 of these 17 cases (cases 7 to 10; in 3 of which adequate treatment had been given) marked atrophic changes were found in the gastric mucosa. It is evident that in these cases liver treatment influenced the blood-forming organs but not the gastric mucosa. It is a curious fact that in 1 of these cases not only the blood count but the tongue had also

become normal, whereas the atrophic gastric mucosa had not responded to liver therapy.

The 6 following cases (cases 11 to 16) have in common the fact that after sufficient treatment the antral mucosa seemed to be normal while some portions of the mucosa of the body presented more or less extensive patchy atrophic areas. In the last of these cases there were superficial gastritis of the fornix and slight patchy gastritis of the body, so that the picture agreed exactly with that in case 6, in which liver therapy was not given. It is not possible to state definitely that in any of these cases the treatment which had altered the blood picture and had kept the patients alive had had any influence on the gastric mucosa.

In 4 patients (cases 17 to 20) the gastric mucosa was entirely normal. This normality must be attributed to the treatment, because in untreated patients a normal mucosa is never observed. Three of these patients had been treated energetically. One of them (case 17) in whom the treatment had been less energetic was examined six times. A normal gastric mucosa was found four times, and marked superficial gastritis was seen on two occasions. (The question of the benign polyps found at each of these examinations will be omitted in this connection.)

If cases 6, 16 and 17 are compared, it must necessarily be concluded that superficial gastritis without atrophy is the primary visible lesion and that atrophic changes develop after this primary superficial inflammation.

In cases 21 to 23 observations were made before and after liver therapy. In case 21 the extensive, complete atrophy of the stomach disappeared after liver therapy except for a few atrophic patches in its highest portion. This observation seems to point to the fact that the normal mucosa seen in cases 17 to 20 was due to the influence of liver therapy; i. e., in some cases of pernicious anemia a previously atrophic mucosa may regenerate to a normal macroscopic aspect with liver treatment. These observations correspond with those made by Jones, Benedict and Hampton.[18] It should be emphasized again that this regeneration takes place in only a fraction of all the cases studied.

One patient (case 22) was observed three times and always showed the same phenomenon, though to a lesser extent. The antral mucosa, which at first was markedly atrophic, became normal, whereas the body mucosa remained atrophic. We have gained the impression that the regenerative process is more likely to develop in the antrum than in the body. It should be remembered that in one third of the untreated patients the antrum was not affected at all, the pathologic changes being present only in the body.

Finally, 1 patient (case 23) not only failed to show any improvement of the gastric atrophy under entirely satisfactory treatment, but,

on the contrary, when the blood picture had become normal, the atrophy had increased considerably in size. This observation, in our opinion, speaks most definitely against the mere regressive degenerative character of the gastric atrophy in pernicious anemia. In the same case, hypertrophic changes of the antrum developed. It may be that they constitute a kind of compensatory reaction; but it seems to us better not to speculate about their nature, since their exact character was not proved by repeated observations or by histologic study.

In 2 cases (cases 6 and 17) multiple polyps of the gastric mucosa were observed; in 1 case a solitary polyp was seen (case 11).

2. *Theoretic Considerations.*—The following observations must be considered:

1. No patient with untreated pernicious anemia showed a normal stomach at gastroscopic observation. However, it seems to be certain that the primary visible lesion is superficial gastritis.

2. The more or less extensive atrophic changes are found either throughout the stomach or in the body alone; the antrum sometimes may be free from changes.

3. Sufficient liver therapy may lead to one of three end results with respect to the atrophy: (1) a reversal of the atrophic changes, the gastric mucosa becoming normal; (2) no change, or (3) advancement of the atrophic changes during the treatment.

We know that in pernicious anemia a hormone is missing which may be substituted for by liver therapy. The main source is the gastric mucosa or, more specifically, the mucosa of the antrum and the duodenum ("pyloric organ," Brunner glands); although it may be admitted that other portions of the stomach or even of the intestine or other organs may produce minor quantities of this hormone (see the fundamental papers by Whipple and Robscheit-Robbins,[18] Minot and Murphy [23] and Castle [9]). Since changes of the gastrointestinal mucosa are found in all cases of pernicious anemia, a connection between these two facts appears probable. Faber [10] drew the apparently inescapable conclusion that chronic gastritis is the primary disease affecting the function of the "pyloric organ," thereby producing the clinical picture of pernicious anemia. Although this theory seems to be sound, it nevertheless cannot be reconciled with our observations. It is true that the changes observed are inflammatory changes. Nevertheless, they cannot be the cause of the destruction of Castle's intrinsic factor, because (1) superficial as well as atrophic changes are most pronounced in the upper

23. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia: Study of One Hundred and Five Cases, J. A. M. A. **89:** 759 (Sept. 3) 1927.

portions of the stomach and often are entirely absent from the antrum and (2) in some cases (the cases reported on by Jones, Benedict and Hampton [18] and our own cases) complete reversion of the atrophic process can take place. It is almost unbelievable that an inflammatory process of unknown origin should destroy the gastric mucosa to such an extent as to prevent the formation of a hormone and that this same inflammatory process should be healed by the administration of exactly the same hormone.

The only possible conclusion is that in pernicious anemia one is dealing with two different diseases of the gastric mucosa: a primary disease, probably invisible and concerning those portions of the gastric mucosa which form the intrinsic "antianemic" factor; and a secondary disease, developing because of the lack of the intrinsic factor which produces the typical syndrome, namely, pathologic changes in the tongue, the pharynx, the blood and the nervous system (Guillaume [24]). These secondary changes respond in a different way to the administration of the missing hormone: The blood may become normal, whereas the inflammation may remain stationary or may even advance; the blood picture and the tongue may become normal, the gastric atrophy remaining unchanged; or the blood picture may become normal, and the gastric mucosa, at the same time, may become normal, too.

How can a deficiency state produce inflammation of a mucous membrane? The best paradigm of such a condition is xerophthalmia. It is well known that xerophthalmia is caused by lack of vitamin A. It can be produced artificially and studied microscopically at an early stage, a status which is impossible in the mucosal manifestations of pernicious anemia. The following progression has been established: primary degeneration of the epithelium cells of the cornea [25] leading to secondary inflammation. We believe that the gastric mucosa follows a similar evolution in pernicious anemia. The first event is the dysfunction of the cells which produce the intrinsic factor. We do not know the cause of this dysfunction. The second and consequent event is a degenerative process of the surface epithelium of the gastric mucosa. This stage can never be observed, since it occurs so early. It is therefore not known whether it would be possible to see the degeneration macroscopically, for instance, because of a loss of transparency. A degenerated surface epithelium may immediately give way to secondary inflammation due to chemical irritation or to bacteriologic infection. Superficial gastritis develops, and this may sometimes be observed gastroscopically. The

24. Guillaume, A. C.: Etude physiopathologique sur le rôle hématopoiétique de l'estomac, Arch. d. mal. de l'app. digestif **26**:241, 1936.

25. Tassman, I. S.: Dietary Deficiency and Ocular Disease, Arch. Ophth. **8**: 580 (Oct.) 1932.

tendency to heal, if the surface epithelial cells have regained their protective power as a result of adequate treatment, seems to be much greater in the antrum than in the body. If no therapy is given, the superficial gastritis usually turns into atrophic gastritis. This development is common in cases of nonspecific chronic superficial gastritis without pernicious anemia and has been described.[26] After the administration of adequate treatment at this point, two types of development have been observed. Either the gastric cells are irreparably damaged by the inflammation, and the atrophy persists or even proceeds; or there are enough normal cells left to serve as a nucleus for complete regeneration.

We have already mentioned that the fact that the atrophy may proceed, in spite of sufficient elimination of the deficiency state, seems to us to prove its inflammatory rather than its purely degenerative nature. If this were merely a regressive process due to a deficiency state, one could expect that it would become stationary after the elimination of the deficiency state. It is impossible for us to understand how such a regressive process could become worse after the elimination of the deficiency state. On the other hand, if it is assumed that the atrophic process is not a degenerative but an inflammatory one, the difficulty of explaining the phenomenon is eliminated. An inflammation depending on factors other than the deficiency state alone (infection or irritation) could proceed even after sufficient amounts of the missing hormone had been given. We believe that the observations in case 23 are definite proof that the atrophic changes found in patients with pernicious anemia are of inflammatory rather than of purely degenerative origin.

The question arises: What happens to the gastric function during regeneration of the mucous membrane? Three possibilities must be considered: 1. The anacidity is a consequence of the existing gastritis; anacidity is often found in superficial as well as in atrophic gastritis. One would conclude that the function of the acid-secreting cells should return after the regeneration of the gastric mucosa. Faber and also Alsted [27] have mentioned such cases, but unfortunately gastroscopic examinations were not made. 2. The acid-secreting cells are damaged by the same process which caused the cessation of the secretion of the intrinsic factor. In that case, reparation of function does not seem to be likely. 3. Or, finally, the anacidity is a constitutional hereditary anomaly

26. Schindler, R., and Ortmayer, M.: Classification of Chronic Gastritis with Special Reference to the Gastroscopic Method: Study Based on One Thousand Two Hundred Cases, Arch. Int. Med. **57**:959 (May) 1936. Schindler.[12] Schindler, Ortmayer and Renshaw.[20a]

27. Alsted, G.: On Free Hydrochloric Acid in the Stomach in Pernicious Anemia, Acta med. Scandinav. **82**:288, 1934.

(Hurst[11]), a factor essential for the origin of pernicious anemia. It seems that in families of patients suffering from pernicious anemia, not infrequently other members are found who also present histamine-fast anacidity. Since so few cases have been reported in which the anacidity disappeared after the institution of liver therapy, whereas complete regeneration of the gastric mucous membrane certainly is not a rare event; we are more inclined to accept one of the two latter theories than to attribute the anacidity to the gastritis.

It has been mentioned that the deficiency state leads to a definite syndrome, consisting of inflammation and atrophy of the tongue, the pharynx, the stomach and the intestine and changes in the blood picture and in the nervous system, especially combined degeneration of the spinal cord. However, it is likely that there are cases in which the same deficiency does not produce all the links of this chain. The most dangerous one, the dysfunction of the hemopoietic apparatus, may be missing. There are perhaps cases in which severe atrophy of the gastric mucosa is found linked with combined degeneration of the spinal cord. One should remember the fact that atrophic gastritis is found in sprue and that this disease responds to liver treatment. In addition, we were able to present a case (case 24) in which severe atrophic gastritis responded to liver therapy, with complete regeneration; in this case only scarcely perceptible signs of degeneration of the spinal cord and only once slight anisocytosis were noted. It remains to be seen in how many cases atrophic gastritis (epigastric distress, belching, fulness, general weakness and nervousness—common symptoms of atrophic gastritis) can be healed by the administration of liver.

It is well known that mucosal tumors, polyps and carcinoma are frequent in pernicious anemia, so that it is not surprising that we found typical apparently noninflammatory adenoma in 3 of our cases.

SUMMARY

Gastroscopic observations are presented for 23 patients with pernicious anemia. Nine of these patients were seen before any treatment had been given, 14 were observed only after adequate treatment and 3 were examined before and after treatment.

All untreated patients presented superficial gastritis, superficial plus atrophic gastritis or patchy or diffuse atrophy.

After treatment in 4 cases no marked improvement of the condition of the gastric mucosa was found, in 1 case there was definite progression of the atrophy, in 7 cases the mucosa of the antrum was found to be normal, in 1 case there was almost complete regeneration and in 4 cases all portions of the gastric mucosa became normal.

These facts can be explained only by the assumption that in pernicious anemia two separate diseases of the stomach are present. Primarily there is dysfunction of the cells which produce the "antianemic" factor. Secondarily there follows degeneration of the surface epithelium, with superimposed genuine inflammation, which may or may not heal when the deficiency state is eliminated.

The secondary inflammation usually is combined with a similar disorder of the tongue and of the intestine, with dysfunction of the hemopoietic apparatus and combined degeneration of the spinal cord. However, the absence of the "antianemic" factor may sometimes lead to severe but reversible atrophic gastritis, without disease of the blood. If this observation is confirmed, the expression antianemic must be replaced by another term.

Probably in many cases atrophic gastritis is due to some kind of deficiency state and in some of them to the lack of the "antianemic" factor. This disease should be diagnosed by the use of the gastroscope, and in each case that is discovered liver therapy should be given tentatively. Gastroscopic check of the result of therapy is necessary.

The frequent incidence of mucosal polyps of the stomach in pernicious anemia is corroborated by our observations.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

RUSSELL M. WILDER, M.D., PH.D.
AND
DAVID I. RUTLEDGE, M.D.
Fellow in Medicine, the Mayo Foundation.
ROCHESTER, MINN.
AND
DWIGHT L. WILBUR, M.D.
SAN FRANCISCO

I. DISEASES OF METABOLISM

BY DR. WILDER AND DR. RUTLEDGE

ENDOCRINE RELATIONS IN DIABETES MELLITUS

The primary contribution of the past year to the physiology of diabetes mellitus was the demonstration by Frank George Young,[1] of University College, London, that *lasting* diabetes can be produced in dogs by injection of anterior pituitary extract. The preliminary report appeared in August 1937; publication of satisfactory details was made in March 1938. Hyperglycemia and glycosuria had been obtained before with similar extracts by Evans and his associates [2] (1932) and by others, including Houssay and his colleagues,[3] but the glycosuria in their experiments was impermanent and persisted only as long as daily injections were maintained, never much longer. Such transitory glycosuria, even with hyperglycemia, does not constitute diabetes. It can be provoked in otherwise normal men or animals by overfunction of the thyroid or adrenal glands, by irritations of the central nervous system or by drugs, particularly by anesthetics. The outstanding characteristic of true diabetes is its permanency; in fact, reports of cure of diabetes mellitus are extremely rare and always doubtful. The significance of

From the Department of Medicine, the Mayo Clinic (Dr. Wilder), and Stanford University School of Medicine (Dr. Wilbur).

1. Young, F. G.: Permanent Experimental Diabetes Produced by Pituitary (Anterior Lobe) Injections, Lancet **2**:372-374 (Aug. 14) 1937; The Diabetogenic Action of Crude Anterior Pituitary Extracts, Biochem. J. **32**:513-523 (March) 1938.

2. Evans, cited by Young.[1]

3. Houssay, cited by Young.[1]

the contribution of Young is that for the first time since the epoch-making discovery of von Mering and Minkowski [4] (1889) diabetes has been produced experimentally which conforms to clinical diabetes in its primary characteristic, namely, *permanency*.

Unsatisfactory results were obtained by Young in many experiments with mice, rats, guinea pigs, rabbits and cats; but with dogs and comparably large amounts of material the effects were unmistakable. Corresponding injections, for control, of extracts of muscle, liver and denatured pituitary substance gave completely negative results. Not all the dogs reacted equally; no result was obtained with 1 pregnant bitch, and only in 5 of the 6 dogs receiving suitable amounts of the extract were the diabetic manifestations lasting. The extracts were prepared from fresh pituitaries, frozen immediately in solid carbon dioxide and dissected in the frozen state. The anterior lobes were minced while still frozen, were ground with sand and ice-cold salt solution (2 cc. per gram of pituitary) and after standing one hour were centrifuged in the cold room. The supernatant solution was injected intraperitoneally, without further attempt at sterility than that provided by the continuous low temperature. Extracts mildly acid and those mildly basic were equally active. Extracts of acetone-desiccated glands were somewhat less potent.

The amounts of material required were enormous, as appears from the following description of a typical experiment given by Young:

> The daily intraperitoneal administration of 10 g. equivalent of saline extract was begun on the first day of experiment, after an initial control period. Polyuria and ketonuria appeared on the 3rd day but the excretion of sugar did not begin until the 5th day of injection when the daily pituitary injection was increased to 15 g. equivalent of extract. During the daily injection of 15 g. equivalent of extract the glycosuria increased until the 7th day of injection after which it began to decrease, finally disappearing on the 11th day, at which time the urine had become free from ketone bodies. It is interesting to note that at this time the daily urine volume was still much above the pre-injection level. The phenomenon of the disappearance of the symptoms of diabetes, despite the continued daily administration of that dose of extract which induced the appearance of diabetes, has occurred in all animals showing a diabetic response, including species other than the dog. If the daily administration of 15 g. equivalent of extract had continued from the 11th day onward it seems most improbable that glycosuria would have reappeared. Nevertheless when the daily dose was increased to 20 g. equivalent, on the 11th day glycosuria and ketonuria reappeared to fall again to zero on the 16th day of injection.
>
> It was clearly of interest to determine if a daily level of injection could be reached which was of sufficient magnitude to prevent the animal becoming resistant to the diabetogenic action of the extract. With this object the daily dose was increased to 25 g./ day on the 16th day of injection. This resulted in the reap-

4. von Mering, J., and Minkowski, O.: Diabetes mellitus nach Pankreas-exstirpation, Arch. f. exper. Path. u. Pharmakol. **26**:371-387, 1890.

pearance of glycosuria which rose to 130 g./ day on the 21st day, thereafter declining to about 50 g./ day without showing any tendency to diminish further. On the 24th day the ketonuria reached a high level, and on the 26th day the animal passed into a semicomatose condition. At this time the CO_2-combining power of the blood was 29 vol. % compared with the normal value for the dog of 40 vol. %. Injections were stopped on this day and the ketonuria subsequently rapidly decreased, but the glycosuria persisted, and, 4 weeks after injections had ceased, reached 264 g./ day.

The subsequent history of this animal has been described elsewhere (Young,[1] 1937). The observations of Young have been confirmed by Lukens,[5] of the University of Pennsylvania, and by Best,[6] of Toronto.

The histologic structure of the pancreas and other organs in 6 of the dogs has been fully described by Richardson, of the Department of Anatomy, University College, London, and Young.[7] Their summary follows:

1. The pancreatic islets of two dogs, killed during a period of daily injections of a diabetogenic anterior pituitary extract, showed cellular proliferation and hydropic degeneration in individual islet cells.

2. The pancreas of a dog, which had been diabetic for ten months after cessation of pituitary injections, and which probably died in diabetic coma, contained no detectable normal islet tissue. The islets were completely hyalinised. Pancreatic tissue was obtained from a second dog, which had been diabetic for nearly ten months after cessation of injections, by biopsy operation during a period of insulin therapy. There were some normal islets, but the majority showed varying grades of depletion of cytoplasmic granules in the beta cells. Only very few of the islet cells of this dog exhibited hydropic degeneration.

3. One dog, the only one in six which failed to become permanently diabetic following treatment with suitable anterior pituitary extracts, had, one month after the cessation of pituitary injections, islets of Langerhans which appeared to be normal in every respect.

4. It seems possible that there are three types of response of the islet cells to the injections of anterior pituitary extract: (*a*) proliferation, (*b*) hydropic degeneration of some beta cells, (*c*) disappearance of the granules in the cytoplasm of other beta cells. Hyalinisation may finally occur. Hydropic degeneration was not a prominent feature of the islets of the two permanently diabetic dogs.

5. Proliferation of the islet cells, which was also observed in the pancreas of the rat (Richardson and Young, 1937) may precede, in the dog, the exhaustive or degenerative changes which accompany the onset of permanent diabetes.

6. The other endocrine organs of those dogs in which they were examined showed no striking histological changes.

One of us (Wilder) was shown the sections of the pancreas of 1 of Lukens' dogs that had died of peritonitis. The infection resulted

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5. Lukens: Personal communication to the authors.

6. Campbell, J., and Best, C. H.: Production of Diabetes in Dogs by Anterior-Pituitary Extracts, Lancet **1**:1444-1445 (June 25) 1938.

7. Richardson, K. C., and Young, F. G.: Histology of Diabetes Induced in Dogs by Injection of Anterior-Pituitary Extracts, Lancet **1**:1098-1101 (May 14) 1938.

from repeated injections of unsterilized extract before severe diabetes had developed. These sections revealed what was interpreted as hyperplasia, as well as hydropic degeneration of the insular epithelium.

In the experiment described by Best [6] the dog continued to excrete sugar for fifty-eight days after injections were discontinued; removal of the pancreas at the end of this time had little effect on the animal's requirement for insulin. In this pancreas the islands of Langerhans showed extreme hydropic degeneration. Furthermore, an assay of the organ revealed a low content of insulin.

The most likely interpretation of these findings is one which harmonizes fully with the unitary hypothesis of diabetes, namely, that the action of the secretion of the anterior lobe of the pituitary is antagonistic to insulin and that a balanced output of this secretion of the pituitary and of insulin is normally maintained by the respective glands of origin, so that if one gland oversecretes, the other in consequence is driven to greater activity. The insular epithelium of the pancreas normally possesses a reserve capacity sufficient to meet all ordinary and almost all extraordinary demands; but that it can be exhausted, if driven to extremes, with resulting hydropic degeneration followed by atrophy, was clearly shown by F. M. Allen's [8] observation of hydropic degeneration and atrophy of the islands in the remnants of pancreas left after partial pancreatectomy. When dogs are deprived of more than nine tenths of the pancreas, the remaining insular tissue, since the tail of the pancreas contains much more insular epithelium than the head and only a part of the head is left, represents much less than a tenth of the original insular epithelium. In such animals heavy feeding (of sugar) causes hydropic degeneration of the island cells and progressively intensifying diabetes. When the pancreas is intact and possessed of its usual reserve, neither hydropic degeneration nor diabetes results from feeding sugar or even from continuous injections of large amounts of dextrose for days and weeks (unpublished observations). Nor did the injection of pituitary extract, in the enormous doses given by Young, push to extremes the pancreatic reserve of the mice, rats, guinea pigs, rabbits, cats and 1 of the dogs. In many of his dogs it did, as was evidenced; and in a few dogs extreme insular degeneration (hydropic) with consequent atrophy was produced, resulting in lasting diabetes. Thus only by exhausting the pancreas does the anterior lobe of the pituitary cause diabetes, and since in clinical diabetes there is no reason to suppose that the pituitary ever could supply amounts of its secretion comparable to the gigantic doses of extract (representing the glands of

8. Allen, F. M.: Experimental Studies in Diabetes (Series III). The Pathology of Diabetes: I. Hydropic Degeneration of Islands of Langerhans After Partial Pancreatectomy, J. Metab. Research **1**:5-41 (Jan.) 1922.

25 oxen) given daily by Young, there is every reason to suppose that a primary defect of the pancreas must preexist in those few cases of diabetes in which pituitary overactivity legitimately can be suspected (acromegaly; menopause). If this explanation proves to be correct, it will be necessary to return to the point of view that a few, mostly clinicians, have never abandoned, namely, that some defect of the insular epithelium is requisite to the development of true diabetes mellitus.

The Pituitary in Clinical Diabetes.—Davidoff [9] found frank diabetes in 12 of 100 of Cushing's cases of acromegaly. A later follow-up study of 150 of Cushing's cases by Root [10] revealed a slightly higher incidence. Our own experience, recently reviewed (unpublished), shows in 218 cases of acromegaly a maximum incidence of diabetes of 9.2 per cent (20 cases). The figure probably is high. In 3 instances the diagnosis of acromegaly was doubtful, and in 3 others the diabetes amounted to only an alimentary glycosuria. If these cases are excluded the incidence was only 6.4 per cent. This is not impressive, particularly in view of the fact that the onset of the diabetes in an indeterminable number of the cases certainly preceded that of acromegaly. The figure is scarcely higher than that found for diabetic patients of the same age groups with adenomatous goiter with hyperthyroidism.

In many of these 218 cases of acromegaly the process undoubtedly was burned out before the patient came for examination, and glycosuria of sufficient intensity to be interpreted as diabetes might have existed in a previous more active stage of hyperpituitarism. It is questionable, however, whether diabetes characterized by such impermanence deserves to be called diabetes mellitus. In other cases diabetes may have developed since examination, but the same could be expected in any group of nondiabetic patients and particularly in a group, such as this, containing many patients with elevation of the basal metabolic rate.

In this connection it is important also to note that nonacromegalic tumors of the hypophysis may provoke glycosuria by pressure on or invasion of the subthalamic region of the brain. Colwell,[11] even after an incomplete survey, found 38 cases in which nonacromegalic lesions of or near the hypophysis were accompanied by glycosuria or diabetes, and he suggested that this number compared favorably with the incidence of glycosuria and diabetes in patients with acromegaly. Looked at the other way, the incidence of acromegaly in the diabetic patients at the Mayo Clinic has been less than 0.3 per cent, representing not more than 1 acromegalic patient among every 469 diabetic patients.

9. Davidoff, L. M.: Studies in Acromegaly: III. The Anamnesis and Symptomatology in One Hundred Cases, Endocrinology **10**:461-483 (Sept.-Oct.) 1926.

10. Root: Personal communication to the authors.

11. Colwell, A. R.: The Relation of the Hypophysis to Diabetes Mellitus, Medicine **6**:1-39 (Feb.) 1927.

It is often stated that diabetes associated with acromegaly runs an irregular course, but Colwell, in his critical review of the literature, did not find it so; and in our more recent experience as well as in our earlier experience, reported by Yater,[12] acromegalic patients with severe diabetes have responded to dietetic management and insulin in no unusual way. However, Berg,[13] in a study of the reaction to dextrose tolerance tests and to insulin in 6 cases in which there were the characteristic features of acromegaly, found 3 in which the extent of the lowering of the blood sugar content by insulin was much less than normal, and in these cases the blood sugar curves were of the diabetic type. Since the findings in the other 3 cases were not abnormal, he concluded that the "anti-insulin factor" of the pituitary may or may not be involved in the presence of adenomas affecting the growth factor. Mauriac and Broustet,[14] in their study of a patient in whom symptoms of diabetes and those of acromegaly developed simultaneously, found the diabetes at first to be perfectly amenable to treatment with not more than 40 units of insulin, although later, after roentgen irradiation of the region of the pituitary, 80 to 120 units was needed for control. Also, Flaum,[15] giving insulin and dextrose simultaneously to patients with insulin-sensitive diabetes and to 2 patients with acromegaly and diabetes, obtained evidence of insulin insensitivity in the latter group. Thus some degree of insensitivity to insulin is to be found in some but not all cases of acromegalic diabetes; however, severe insulin resistance in such cases has not been reported, and in all instances of marked insulin resistance, such as occurred in a case reported by Marble,[16] attempts to demonstrate the responsibility of the pituitary have failed.

There is ground for the suspicion that the functional overactivity of the anterior lobe of the pituitary is in part responsible for the unusual frequency of diabetes in older women. However, Pijoan and Zollinger[17]

12. Yater, W. M.: Acromegaly and Diabetes: Report of Six Cases, Arch. Int. Med. **41**:883-912 (June) 1928.

13. Berg, B. N.: Insulin Response in Acromegaly, Bull. Neurol. Inst. New York **6**:178-182 (Aug.) 1937.

14. Mauriac, P.; Broustet, P.; Saric, R., and de Lachaud, R.: Insulinorésistance et radiothérapie dans le diabète acromégalique, Progrès méd., March 19, 1938, pp. 413-421.

15. Flaum, G.: Insulin-Insensitivity: Its Possible Relation to the Pituitary Gland, Endocrinology **23**:630-636 (Nov.) 1938.

16. Marble, A.: Insulin Resistance: Report of a Case of Marked Insensitiveness of Long Duration Without Demonstrable Cause, Arch. Int. Med. **62**:432-446 (Sept.) 1938.

17. Pijoan, M., and Zollinger, R.: Observations on Carbohydrate Metabolism Following Irradiation of the Pituitary Gland, Endocrinology **21**:357-360 (May) 1937.

could obtain no evidence of abnormality of carbohydrate metabolism in a group of 20 otherwise normal women who were subjected to 1,200 to 1,600 roentgens of radiation to the pituitary for the treatment of the menopausal syndrome. Thirty-five per cent had a definite and sustained decrease in the number of flashes, but the blood sugar curves, which in all cases were normal before irradiation, remained so afterward; the sensitivity to insulin was unaltered, and in an isolated examination the rise of the respiratory quotient after the oral administration of dextrose was unchanged.

The Adrenal Gland and Diabetes.—That abnormally mild diabetes follows pancreatectomy in animals when the pituitary also has been removed (the Houssay animal) has now become general knowledge. Reference was made in a previous review [18] (1937) to the cats of Long and Lukens that showed similar amelioration of pancreatectomy diabetes after bilateral adrenalectomy. The two operations, hypophysectomy and bilateral adrenalectomy, seemed to have the same effect, except that the diabetes of the Houssay animal could be greatly intensified by injection of anterior pituitary extract, whereas injecting extracts of adrenal cortex into the cats of Long [19] and Lukens [20] was without any such result. The failure to obtain an increase in the manifestations of diabetes in their animals was puzzling, because much evidence suggested that the ameliorating effect of hypophysectomy in diabetes following pancreatectomy was related to the atrophy of the adrenal cortices which follows that operation. The evidence included the fact that after the adrenals are removed from Houssay dogs, injections of anterior pituitary extract are no longer effective. This has been disputed by Houssay. In any case, positive diabetogenic results with injections of extracts of adrenal cortex were finally obtained by Lukens and Dohan,[21] and the explanations offered for the previous failures were the use of cats in the earlier experiments, an unfavorable species, and their meat diet, rich in potassium. Experiments with dogs showed that adrenal cortex extract is capable of restoring to a considerable extent the diabetes of the adrenalectomized, depancreatized animal.

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18. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **59**:329-364 (Feb.) 1937.

19. Long, C. N. H.: The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes, Medicine **16**:215-247 (Sept.) 1937.

20. Lukens, cited by Long.[19]

21. Lukens, F. D. W., and Dohan, F. C.: Further Observations on the Relation of the Adrenal Cortex to Experimental Diabetes, Endocrinology **22**: 51-58 (Jan.) 1938.

In the meantime, Long, Fry and Thompson [22] have also obtained evidence of diabetogenic activity in cortical extract. They performed partial pancreatectomy on over 100 rats at an age of 25 to 30 days, and about 30 per cent of the animals later exhibited spontaneous glycosuria when fed. These later were adrenalectomized, and if salt was provided abundantly they could be kept in good health. After the adrenalectomy the glycosuria either disappeared or was greatly diminished. It then could be made to reappear or increase if adrenals of 1 day old rats were engrafted or if daily with the drinking water 5 to 10 cc. of a potent cortical extract was administered. Of additional interest is the fact that it also could be made to reappear if 3 mg. of either of the crystalline compounds A and B isolated from adrenal cortex by Kendall and supplied by him was administered *by mouth.* A comparable result was obtained when large quantities of either the extract or the crystalline compounds were given to partially depancreatized, but otherwise normal rats during fasting. Long also has reported that the extract and the crystalline compounds caused in normal rats a marked increase in the glycogen content of the liver and, in a few animals, slight hyperglycemia. The acetone body content of the liver increased, and a few experiments indicated an increase in urinary nitrogen.

Clinical evidence of a role of the adrenal cortex in carbohydrate metabolism is also available. A review of the literature by Duncan and Fetter [23] revealed 8 proved cases of adrenocortical tumor with diabetes, and Long [24] and Lukens [25] found evidence of some impairment of carbohydrate metabolism in half of 55 reported cases of this disease. Our own experience in cases of this type has been relatively large. It comprised, when reported recently by Kepler and Wilder,[26] 2 cases of diffuse hyperplasia of the adrenal cortices and 8 cases of tumor. The diagnoses were confirmed by operation or necropsy. Frank diabetes was present in both cases of diffuse hyperplasia and in 1 of the cases of tumor. In addition, dextrose tolerance tests gave abnormal responses in 2 of the cases of tumor. However, in the 2 cases of hyperplasia, necropsy revealed other involvement of the pancreas (abscess in 1 and carcinoma in the other), and for 2 of the 4 patients with tumor who

22. Long, C. N. H.; Fry, E. G., and Thompson, K. W.: The Effect of Adrenalectomy and Adrenal Cortical Hormones upon Pancreatic Diabetes in the Rat, Am. J. Physiol. **123**:130-131 (July) 1938.

23. Duncan, G. G., and Fetter, F.: Suprarenal Tumor—Hirsutism—Diabetes, M. Clin. North America **18**:261-268 (July) 1934.

24. Long, C. N. H.: Disturbances of the Endocrine Balance and Their Relation to Diseases of Metabolism, Ann. Int. Med. **9**:1619-1627 (June) 1936.

25. Lukens, cited by Long.[24]

26. Kepler, E. J., and Wilder, R. M.: Disturbances of Carbohydrate Metabolism Observed in Association with Tumors of the Adrenal Cortex, Acta Med. Scandinav. (supp.) **90**:87-96, 1938.

were living more than one year after operation the fasting values for blood sugar obtained elsewhere were normal.

THE LIVER AND CARBOHYDRATE METABOLISM

The dictum of Claude Bernard that "the normal blood sugar level is the result of a precise equilibrium between the processes of anabolism (sugar formation by the liver) and catabolism (sugar utilization by the tissues)" has been accepted generally although supported heretofore only by indirect evidence. It now is established for dogs, with data of quantitative significance. Soskin, Essex, Herrick and Mann [27] not only have determined the rate of total flow of blood through the liver of suitably prepared dogs but have measured the arterial and venous components of the total, using for the purpose thermostromuhrs, previously described by Baldes, Herrick and Essex.[28] The stromuhrs were arranged ingeniously so as to record the rate of flow in the hepatic veins and in the portal vein and by difference that in the hepatic artery. The output and intake of sugar by the liver were calculated by correlating the rates of blood flow per minute with determined contents of sugar in the inflowing or outflowing blood. Observations were made during control periods and after intravenous injections of dextrose. Secretion of sugar by the liver occurred in the control periods, whereas after dextrose was injected secretion invariably ceased and retention followed. In the protocols of one experiment the rate of secretion for thirty minutes averaged 18 mg. per minute; the animal weighed 18.9 Kg. and the liver 655 Gm. The maximum rate of retention after intravenous injections of dextrose was 85.5 mg. per minute.

An observation the significance of which was not discussed was that the portal vein or the hepatic artery, in different animals, sometimes carried as much as 90 per cent or as little as 10 per cent of the total amount of blood entering the liver. Such large differences were the exception, but reciprocal variations frequently occurred during the course of an experiment without accompanying variation in the total outflow of blood from the hepatic veins. Also, there were no comments on the fact that the rate of secretion of sugar in the control period of the experiment for which protocols were given, before sugar was injected and at a time when the animal presumably was in a post-absorptive state, was so much less than the rate at which sugar has been shown to disappear from the blood in the hepatectomized dog. By

27. Soskin, S.; Essex, H. E.; Herrick, J. F., and Mann, F. C.: The Mechanism of Regulation of the Blood Sugar by the Liver, Am. J. Physiol. **124**:558-567 (Nov.) 1937.

28. Baldes, E. J.; Herrick, J. F., and Essex, H. E.: A Modification in the Thermostromuhr Method of Measuring the Flow of Blood, Proc. Soc. Exper. Biol. & Med. **30**:1109-1111 (May) 1933.

our calculation, as was stated, the rate of secretion in the control period averaged, for thirty minutes, 18 mg. per minute. This represented only 57 mg. per kilogram of body weight per hour, whereas in the liverless dog the rate of disappearance of sugar is close to 250 mg. per kilogram per hour. Apparently it is unjustifiable to assume, as has been done, that the liver of the intact animal must always secrete sugar during fasting at the high rate of 250 mg. per kilogram per hour to prevent hypoglycemia and to deduce therefrom that the amount of sugar derived from protein is insufficient to prevent the development of hypoglycemia in the intact animal. Even the much lower figure of 57 mg. per kilogram per hour (representing 18 mg. per minute in the control period of this recent experiment) may be erroneously high, since errors of ± 2 per cent are inherent in the clinical determination of the blood sugar content and a 10 per cent error is present in measurements of blood flow with the thermostromuhr. Also, in this experiment the liver presumably was not nearly emptied of its glycogen.

HOMEOSTASIS OF BLOOD SUGAR

As mentioned in a previous review,[29] Soskin and his collaborators found that when the blood sugar value for depancreatized dogs was maintained at a normal level by constant intravenous injections of dextrose and insulin, added doses of dextrose gave normal blood sugar curves. Under the conditions of their experiments extra insulin to provide for the increased intake of dextrose was neither available nor required. The hypothesis that the maintenance of homeostasis of the blood sugar in the normal organism after ingestion of carbohydrate is dependent on the ability of the pancreas to secrete insulin was therefore held to be untenable. Ricketts[30] has challenged this conclusion. His experiments showed that protamine insulin in sufficient doses to hold the blood sugar value at normal levels during fasting would not prevent a hyperglycemic response to ingestion of carbohydrate in cases of severe diabetes or in depancreatized dogs. In cases of mild diabetes, in which supposedly the pancreas is not incapable of responding with secretion of "extra" insulin, the blood sugar curves after ingestion of dextrose were more nearly normal. Soskin and his collaborators postulated the necessity for an adequate supply of insulin but concluded that an extra supply at the time of ingestion of carbohydrate is unnecessary.[29] Ricketts pointed out that his different results probably were

29. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **57**:422-471 (Feb.) 1936.

30. Ricketts, H. T.: Carbohydrate Tolerance After Protamine Insulin: Its Bearing on the Physiology of Insulin Secretion, J. Clin. Investigation **17**:795-801 (Nov.) 1938.

to be explained by differences in experimental procedure. Soskin and his associates were determining what the organism could be made to do under artificial conditions; on the other hand, what Ricketts was studying was what it actually does as a matter of everyday existence. That the homeostatic mechanism of the liver may play an independent part in regulation of the blood sugar is not denied, but in his opinion his experiments indicate that the proper functioning of the liver, under normal circumstances, depends on the availability of an extra supply of insulin at the time of ingestion of carbohydrate.

PATHOLOGY OF DIABETES [31]

A second edition of Warren's [32] now classic work entitled "The Pathology of Diabetes Mellitus" has been based on a larger experience with this subject than any one individual has ever before accumulated. The total number of necropsies on diabetic patients was 484. Nine were on children under 11 years of age, 29 were on older children and adolescents, and 8 were on patients with hemochromatosis. In addition, because, as Dr. Joslin has said in the foreword, the present diabetic patient is "half and half surgical," Dr. Warren has had the opportunity to study nearly as many biopsies as necropsies. "I am thankful," Dr. Joslin has added, "for the training which Dr. Warren received as editor of the volume of Preventive Medicine issued by the Harvard Medical School, because automatically a note of prevention of diabetes and its complications permeates the text." The motto on the wall of Dr. Warren's "modern operating room" betokens this sentiment—*Mortui vivos docent.*

The years that have passed since the publication of the first edition of this book have brought new problems to the attention of pathologists: Are infants of diabetic mothers abnormally large, with hyperplastic islands of Langerhans? What is the nature of the hepatomegaly in diabetic children? Why does arteriosclerosis in the diabetic patient tend to affect, selectively, the intrinsic arteries of the heart and the arteries of the leg? What part in clinical diabetes is played by the pituitary body? These and many other pressing questions have received consideration. Examination of the pituitary body by serial section in 18 cases of diabetes and of random sections of the pituitary body in 26 more cases revealed no constant significant abnormality. Vacuolation of the basophilic cells of the anterior lobe, comparable to that

31. The following review of Warren's book entitled "The Pathology of Diabetes Mellitus" was written for the section on book notices of *The Journal of The American Medical Association.*

32. Warren, S.: The Pathology of Diabetes Mellitus, ed. 2, Philadelphia, Lea & Febiger, 1938.

described by Kraus,[33] also was seen in control cases. The acidophils were normal in number except in 1 instance; adenomatous groups of cells, such as Kraus has stained, were not found.

The increase in size and weight of the liver in diabetes may be due to a variety of conditions and is not always associated with increased accumulation of fat. The content of fluid is important; study of some of the larger livers suggests hydrops of the cells rather than an excess of fat or glycogen. The abdominal pain not infrequently associated with hepatic enlargement in diabetes may result from stretching of the capsule, as suggested by Marble.[34] This implies rapid change of size, perhaps too rapid for deposition of fat, but quite compatible with fluctuation of intracellular fluid. However, at necropsy the total fatty acid in the liver of persons with diabetes was found to range from 4.1 to 10.8 per cent of the wet weight of fresh liver, whereas for persons without diabetes the range was from 2.2 to 4.5 per cent.

The following statements received from Dr. Warren provide a résumé of what he regards as the most significant contents of his book:

With nearly double the number of cases the frequency figures for various pathologic lesions remain substantially as they were in the first edition.

The histologic normality of the pancreas in one-fourth of the cases is confirmed, and thus gives hope of ultimate cure under favorable conditions.

The observations on the incidence of arteriosclerosis and its possible relationship to unbalanced diets have been amplified.

Topics receiving new consideration include ophthalmic pathology, hyperplasia of the island of Langerhans in the infants of diabetic mothers, and medico-legal aspects of diabetes.

Further evidence of regeneration of the pancreas in diabetes has been adduced.

The studies provide evidence that the newer insulins have no harmful effect in therapeutic doses and that the role of the pituitary and of the adrenals in human diabetes is minor.

His book is a compact mass of interesting material of this type. The illustrations are excellent, and the writing is concise and clear. It is to be highly recommended for all students of diabetes and pathology.

THE DIET IN DIABETES

Reference was made in an earlier review to the suggestion of Marks [35] that the anterior lobe of the pituitary may be stimulated by a diet inadequate in carbohydrate, thus accounting for impairment of tolerance for sugar and decreased sensitivity to insulin when the intake of starch and sugar is restricted. Himsworth and Scott [36] subsequently

33. Kraus, E. J., cited by Warren.[32]

34. Marble, cited by Warren.[32]

35. Marks, H. P., cited by Wilder and Wilbur.[18]

36. Himsworth, H. P., and Scott, D. B. M.: The Relation of the Hypophysis to Changes in Sugar Tolerance and Insulin Sensitivity Induced by Changes of Diet, J. Physiol. **91**:447-458 (Jan.) 1938.

obtained other evidence to support this view. In hypophysectomized rabbits the sugar tolerance and insulin sensitivity were found to remain high, irrespective of whether the diet was low or high in carbohydrate; and when extract of the anterior lobe of the pituitary was injected into these animals while they were receiving high carbohydrate diets, impairment of tolerance and sensitivity to insulin occurred, similar to that observed when a low carbohydrate diet was given. It has been indicated, however, by Himsworth that factors other than increased pituitary activity may also be concerned in the effect produced by low carbohydrate diets.

The epidemic of diets high in carbohydrate has not as yet invaded France. Labbé [37] has written critically of the observations of Porges and Adlersberg, advocates of these regimens. Examination of their report, he said, revealed that the same result, in the cases of moderately severe diabetes, would have been obtained more rapidly by another regimen; and in the other cases what was accomplished seemed to be attributable more to insulin than to the regimen. His own experience with the procedure of Porges and Adlersberg has not been favorable. Glycosuria and elevated blood sugar levels resulted. It is an illusion to depend on hyperglycemia provoked by the administration of carbohydrate to stimulate a secretion of insulin. This may be true for healthy men; it is not true for the diabetic patient. The hyperglycemia and glycosuria of diabetes are always a function of a supply of carbohydrate in excess of the capacity of the patient for its utilization.

Newburgh and some of his colleagues,[38] according to F. M. Allen, have merely rediscovered the value of undernutrition in their studies revealing marked gains in tolerance in originally obese diabetic patients whose weight had been rigidly reduced. According to Newburgh,[38] the hyperglycemia and glycosuria of middle-aged, obese patients are complications of obesity; the primary condition is a lessened ability to lay down glycogen, possibly due to deposition of fat in the liver. Study of the respiratory quotients of these patients gave no indication that the derangement was accompanied by a decreased capacity to oxidize dextrose, thereby setting this large group of glycosuric patients (44 per cent of all diabetic patients) apart, in the sense that their ability to utilize dextrose is dependent only on obesity and is corrected by reduction of weight. Allen [39] has maintained that reduction of weight

37. Labbé, M.: Les régimes pauvres en graisses et riches en hydrates de carbone dans le traitement du diabète, Arch. d. mal. de l'app. digestif **28**:209-222 (March) 1938.

38. Newburgh, L. H.; Conn, J. W.; Johnston, M. W., and Conn, E. S.: A New Interpretation of Diabetes Mellitus in Obese, Middle-Aged Persons: Recovery Through Reduction of Weight, Tr. A. Am. Physicians **53**:245-257, 1938.

39. Allen, F. M., in discussion on Newburgh and others.[38]

increases the tolerance in all cases of diabetes and that patients with inherently severe diabetes, in a sufficiently early or latent stage, will show carbohydrate combustion on a par with that of Newburgh's obese patients with mild diabetes. While we find ourselves in full agreement with Allen's interpretation, we nevertheless have profited from the emphasis placed by Newburgh and also by Fetter, Durkin and Duncan [40] on the advantage to be gained by lessening the weight of the obese diabetic patient. If body weight can be reduced to normal, the patient usually requires no insulin, and that this is the treatment of choice for obese diabetic patients is evident from the fact that the loss of weight is in itself desirable.

Arteriosclerosis in Diabetes.—R. D. Lawrence,[41] of London, in a paper to which reference will again be made, expressed his belief that the danger of arteriosclerosis in diabetes has been exaggerated. He entirely disagrees with the current opinion that hypercholesteremia causes it or that a diet high in carbohydrate can prevent it. A clinical survey of 43 of his diabetic children, under treatment with insulin for ten or more years, revealed no evidence of vascular disease, as judged by blood pressure, retinal vessels and roentgenologic examination of the larger vessels, with 1 exception (retinal arteriosclerosis). Many of the children had been fed diets rather low in carbohydrate; in the majority the diabetic condition had seldom been perfectly controlled. The frequent occurrence of arterial occlusive changes is confined almost entirely to middle-aged and elderly diabetic patients who have mild diabetes and do not show marked hypercholesteremia. In these cases Lawrence suggested that a pituitary influence may be responsible. In this type of case relative insensitivity to insulin is found, and control with insulin can best be obtained with a diet low in calories and rather low in carbohydrate, rather than with larger amounts of carbohydrate and more insulin.

INSULIN

Protamine and Other Long-Acting Insulins.—The literature contains an increasingly large number of articles dealing with protamine zinc insulin. For the most part these are repetitious; some are critical, but on the whole those coming from centers where experience in the treatment of diabetes is large confirm earlier reports of benefit. The use of protamine zinc insulin in Germany was delayed owing to the introduction at about the same time of "insulin durant," recommended by

40. Fetter, F.; Durkin, J. K., and Duncan, G. G.: Dietary Versus Insulin Treatment of the Obese Diabetic Patient, Am. J. M. Sc. **195**:781-787 (June) 1938.

41. Lawrence, R. D.: The Treatment of Insulin Cases by One Daily Injection, Acta med. Scandinav. (supp.) **90**:32-53, 1938.

Katsch [42] and Störring.[43] The action of this product is said to extend over two or three days. A disadvantage is the incorporation of the insulin in a mixture of lipoids, which necessitates injection intramuscularly with special syringes. A preparation with which Zirwer,[44] in Frankfort, has been experimenting is "deposulin," a product of the Brunnengröber firm. This is a mixture of insulin and solution of posterior pituitary, the latter constituent by its vasoconstricting effects retarding absorption. Schweers [45] also has written about this preparation. Beckmann and Weitzsäcker,[46] in Stuttgart, investigated simultaneously "deposulin" (Brunnengröber), "adrenalin-insulin-novo," "depotinsulin" (Bayer) and protamine zinc insulin and found the last two to be superior to the others and approximately equal to each other in effect. "Depotinsulin" (Bayer), also referred to by Umber and his associates,[47] is an insulin bound to (adsorbed by) a nonprotein colloid.

Confirmative of the results obtained with protamine zinc insulin by Danish, American and English investigators is a report by Falta,[48] of Vienna, who has recommended (1) early morning injection of protamine zinc insulin, (2) the giving of any supplementary ordinary insulin required before the noon meal, and (3) the administration of a small meal at bedtime. Likewise confirmative have been the observations of Taeger and Danish,[49] of Schittenhelm's clinic in Munich, and those of Umber and his associates,[50] of Berlin. The experience of Umber has covered the use of protamine zinc insulin in 250 cases. However, he entertains some doubt as to the wisdom of adding a protein substance to insulin and has been endeavoring to obtain equal prolongation of the action of insulin by the use of nonprotein colloids.

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42. Katsch, G.; Scholderer, H., and Klatt, K.: Depotinsulin, Ztschr. f. klin. Med. **129**:608-626, 1936.

43. Störring, cited by Katsch, G., and Klatt, K.: Insulin-Depotbehandlung, Med. Klin. **1**:369-370 (March 12) 1937.

44. Zirwer, K.: Beobachtungen über Insulindepotbehandlung, Klin. Wchnschr. **16**:1121-1122 (Aug. 7) 1937.

45. Schweers, A.: Klinische Untersuchungen zur Behandlung des Diabetes mellitus mit Depotinsulin "Insugerman," Klin. Wchnschr. **16**:392-396 (March 13) 1937.

46. Beckmann, K., and Weitzsäcker, J.: Klinische Erfahrungen mit verschiedenen Depotinsulinen, Klin. Wchnschr. **17**:1321-1325 (Sept. 17) 1938.

47. Umber, F.; Störring, F. K., and Föllmer, W.: Erfolge mit einem neuartigen Depotinsulin ohne Protaminzusatz (Surfen-Insulin), Klin. Wchnschr. **17**:443-446 (March 26) 1938.

48. Falta, W.: Ueber Protamin-Zink-Insulin, Klin. Wchnschr. **16**:1633-1639 (Nov. 20) 1937.

49. Taeger, H., and Danish, L.: Klinische Erfahrungen mit Deposulin, Klin. Wchnschr. **16**:1639-1642 (Nov. 20) 1937.

50. Umber, F.; Störring, F. K., and Glet, E.: Klinische und ambulante Erfahrungen mit verschiedenen Insulindepotpräparaten an 250 Diabetikern, Klin. Wchnschr. **17**:190-196 (Feb. 5) 1938.

Boller,[51] from Eppinger's clinic in Vienna, has described 2 fatal cases with autopsies in which death was attributed to overdosage with protamine zinc insulin. In one of these, metastatic carcinoma of the adrenal glands explained the absence of all antagonism to insulin; in the other case, nothing could be found to account for the fatality. In both cases, and in no others in which protamine zinc insulin was used, a soft, pitting edema of the legs developed a few days before death and disappeared shortly before death. This was the only untoward symptom and suggested that this type of edema may be regarded as a warning of dangerous hypoglycemia.

Somogyi [52] has been studying the pendulum-like fluctuations which normally occur in the blood sugar level after administration of dextrose. In dogs and man directly after the hypoglycemic phase of a blood sugar curve, secondary hyperglycemia frequently is encountered before the fasting level is reestablished. In diabetes the prevalence of hyperglycemia attests to dislocation of the normal enzymatic balance of liver glycogen ⇄ blood sugar, in the direction of blood sugar; and when to this the stimulating effect of hypoglycemia is added, the swing, compensatory to any hypoglycemia, may be grossly exaggerated. In a patient under treatment with insulin the glycosuria accompanying the upward swing of the blood sugar level may prompt the physician or patient to increase the dose of insulin, whereby the pendulum effect is further aggravated and results, in Somogyi's opinion, in aggravation of the diabetes. Bowcock and Wilkinson [53] also have been discussing this phenomenon. They have called it the insulin paradox, because under these circumstances increasing the dose of insulin may be ineffective in preventing glycosuria. We recently saw a patient who, because of the persistence of traces of sugar in diurnal specimens of urine, had gradually increased his doses of protamine zinc insulin from 15 to 80 units a day. Fortunately or unfortunately, he was resistant to most of the symptoms of insulin reaction, although he complained of dull headaches. We ordered an immediate reduction of the dose to 20 units, and although the same diet was consumed, the glycosuria, to the patient's great surprise, was immediately controlled.

51. Boller, R., and Pilgerstorfer, W.: Die Hypoglykämie bei Protamin-Zink-Insulinanwendung, Klin. Wchnschr. **17**:1065-1068 (July 30) 1938.

52. Somogyi, M.: Hyperglycemic Response to Hypoglycemia in Diabetic and in Healthy Individuals, Proc. Soc. Exper. Biol. & Med. **38**:51-55 (Feb.) 1938.

53. Bowcock, H., and Wilkinson, C.: Solution of Zinc-Insulin Crystals Versus Regular Insulin and Protamine Zinc Insulin, J. M. A. Georgia **27**:351-355 (Sept.) 1938. Bowcock, H.: Solution of Zinc-Insulin Crystals—A New Therapeutic Agent: Comparison with Unmodified and Protamine-Zinc Insulin, ibid. **27**: 361-363 (Sept.) 1938.

From England, in a volume entitled "Medical and Physiological Papers," happily dedicated to Dr. H. C. Hagedorn, are articles on protamine zinc insulin by Lawrence [41] and Graham.[54] Lawrence described more fully his method of administering protamine zinc insulin and ordinary insulin in one syringe. The soluble insulin should be drawn into the syringe *first,* "as it does not matter if a trace of acid insulin from the needle enters the buffered protamine bottle, whereas the entry of alkaline material to the acid bottle may make the soluble insulin alkaline and inert by the end of the bottle." In the mixture some of the soluble insulin disappears (10 to 20 per cent), but his case reports indicate that irregularities of action from day to day are no more conspicuous than when the two insulins are injected into separate sites. A stable preparation of protamine zinc insulin and soluble insulin in one bottle has the disadvantage that the fixed proportion is not the best for all patients.

Even with this treatment it rarely is possible to keep the urine constantly free from sugar without risk of hypoglycemia. However, Lawrence has permitted some glycosuria in practically all his cases and "has learned to reduce the insulin if all the urine tests are sugar-free for even one and certainly for two days." In his opinion, "if the patient never passes sugar after supper or before breakfast, the basal dose is too high and should be reduced, perhaps by 4 units; if he never passes sugar after breakfast the soluble insulin should be reduced." In the majority of cases, severe diabetes is kept under reasonable control with one dose of mixed insulin a day. In very severe diabetes other arrangements have been necessary. Variation of method to suit each individual case gives the best individual results, but "unfortunately intense personal study is not available for most cases and some simple and dogmatic method suitable for the majority must be preached." This apology applies also to the description of the procedure used in the Mayo Clinic,[55] which, except that the two types of insulin are not mixed in one syringe, is much like that described by Lawrence.

The ideal in the use of insulin is to imitate the action of the normal pancreas. This, as Lawrence [56] suggested, probably involves (1) a small continuous secretion of insulin, and (2) increased secretion after meals to deal with ingested carbohydrate. No one type of insulin has been prepared which can imitate both aspects of natural function. The slowly acting preparations provide well for the small continuous supply

54. Graham, G.: The Use of a Mixture of Ordinary and Protamine Insulin, Acta med. Scandinav. (supp.) **90**:54-63, 1938.

55. Wilder, R. M.: A Primer for Diabetic Patients, ed. 6, Philadelphia, W. B. Saunders Company, 1937.

56. Lawrence, R. D., and Archer, N.: Some Experiments with Protamine Insulinate, Brit. M. J. **1**:747-749 (April 11) 1936.

required for controlling endogenous production of sugar, but if given in doses large enough also to control the glycosuria which follows meals, they will provoke hypoglycemia. For meeting the increased requirement after the taking of food, in all but relatively mild diabetes, additional supplementary insulin that acts more quickly is necessary.

Graham [54] likewise has found advantage in giving protamine zinc insulin and ordinary insulin together in one syringe. He too appreciates that some change probably takes place in the insulins when they are mixed, but since the same change occurs each day the effect, he has stated, is not so haphazard as it appears. Graham also has commented on the irregularity of control obtained in cases of severe diabetes but has found this to be no more marked with protamine zinc insulin than it is with ordinary insulin. Therefore, he has attributed it not so much to varying rates of absorption of insulin but to the disease, which one day causes a greater demand for insulin and another day a smaller one. Also, Graham, like many others, has come to believe that some hyperglycemia and glycosuria are preferable to the use of excessive doses of insulin, which, although not provoking typical hypoglycemic attacks, causes lack of energy, depression and headache. These symptoms may occur with a normal blood sugar value and may be completely relieved if the dose of insulin is reduced and the blood sugar value is allowed to rise.

Oral Administration of Insulin.—Efforts to protect insulin from the action of the enzymes of the gastrointestinal tract so as to permit its administration by mouth in the treatment of diabetes heretofore have been unsuccessful. That insulin is able to pass the intestinal barrier has been shown, however, by numerous investigators, using isolated loops of bowel, and J. R. Murlin and his associates [57] have presented evidence of activity when insulin, in preparations containing hexylresorcinol, was given perorally to depancreatized dogs. Clinical results with a different preparation have now been reported by Lasch and Schönbrunner.[58] These writers have found that acid organic dyes, such as congo red and trypan red, will protect insulin from disintegration by pepsin and that individual basic dyes, among them malachite green and rhodamine, similarly will protect it against trypsin. The

57. Daggs, R. G.; Murlin, W. R., and Murlin, J. R.: Effect of Hexylresorcinol upon Absorption of Insulin from the Gastro-Intestinal Tract of Dogs, Am. J. Physiol. **120**:744-749 (Dec.) 1937. Murlin, J. R.; Young, L. E., and Phillips, W. A.: New Results on the Absorption of Insulin from the Alimentary Tract, abstracted, Science **86**:412 (Nov. 5) 1937.

58. Lasch, F., and Schönbrunner, E.: Experimentelle Untersuchungen über perorale Insulintherapie unter Beigabe organischer Farbstoffe, Klin. Wchnschr. **17**:1177-1180 (Aug. 20) 1938.

addition of saponin to insulin was found by Walton and Basset [59] to increase absorption in Thiry fistulas, and with tablets containing saponin, trypan red, malachite green and dry insulin Lasch and Schönbrunner have conducted experiments which gave impressive results. Clinical trial of this preparation has been obtained in several German clinics, among them Eppinger's clinic in Vienna. Forty diabetic patients were given the tablets for limited periods in amounts representing doses of insulin varying from 60 to 300 units daily. Data regarding 8 of these patients are included in the report. The disease in most of them was severe, necessitating for its control the use of 45 to 60 units of insulin injected subcutaneously. The equally effective oral doses of insulin were from two to four times as large. The necessary inclusion of saponin limits the usefulness of the preparation; and some doubt as to the safety of long-continued administration of the dyes named may be expressed. No serious side effects were observed from the doses used, but nausea, vomiting and diarrhea, referable exclusively to the amount of saponin, were encountered. Some patients proved to be more sensitive to the disturbing effects of saponin than others. Two patients, however, had been treated for six and 1 patient for eleven months without the development of any disagreeable symptoms. The report was conservative. The authors claimed to have shown conclusively that insulin is absorbed and active when given by mouth, according to the procedure described, but they reserved judgment as to the clinical usefulness of the preparation until it has received wider clinical trial.

Sensitivity to Insulin.—In an earlier review [13] attention was called to the contradiction between the conclusions of MacBryde,[60] using a modification of the Radoslav [61] procedure as a means of determining sensitivity to insulin, and those of Himsworth.[62] The subject has received further study by Klatskin,[63] as well as by Burgert, Scott and Nadler.[64] Klatskin studied 50 patients with diabetes with respect to their response to a standard dose of insulin, and with the MacBryde-Radoslav procedure found wide variation in the percentage of fall of

59. Walton and Basset, cited by Lasch and Schönbrunner.[58]

60. MacBryde, C. M.: Response to Insulin as an Index to the Dietary Management of Diabetes, J. Clin. Investigation **15**:577-589 (Sept.) 1936.

61. Radoslav, C. S.: Ueber die Wirkung des Insulins auf den Blutzucker beim Menschen, Wien. Arch. f. inn. Med. **8**:395-412 (July) 1924.

62. Himsworth, H. P.: Diabetes Mellitus: Its Differentiation into Insulin-Sensitive and Insulin-Insensitive Types, Lancet **1**:127-130 (Jan. 18) 1936.

63. Klatskin, G.: The Response of Diabetics to a Standard Test Dose of Insulin, J. Clin. Investigation **17**:745-750 (Nov.) 1938.

64. Burgert, P.; Scott, R., and Nadler, W. H.: A Comparison of Tests for Insulin Sensitivity, Proc. Central Soc. Clin. Research, 1938, p. 23.

the blood sugar value (between 30 and 85 per cent). However, no sharp cleavage was apparent between groups of patients, and no significant relation appeared between sensitivity to insulin and clinical characteristics or response to high carbohydrate diets. Burgert and his associates applied the insulin tolerance test of MacBryde to 14 patients, who previously had been tested with regard to insulin sensitivity by the Himsworth procedure, and found no dependable correlation. One patient was unmistakably insensitive by both the MacBryde and the Himsworth method; otherwise the correlation was extremely poor, and in individual cases reversibility of sensitivity seemed to occur. The conclusion was reached that no justification exists at present for the classification of diabetes into types on the basis solely of sensitivity or insensitivity to insulin.

PROGNOSIS IN DIABETES

Diabetes ranks with cancer, syphilis and tuberculosis as a problem worthy of attention by agencies of public health and others with interest in preventive medicine. From the point of view of prevention it differs from tuberculosis and syphilis in that eradication of the cause of the disease offers greater difficulties, but in this respect it is no more discouraging than cancer. However, from the point of view of what can be done to protect the affected person from resulting disabilities, the results obtainable in diabetes are far greater than those possible in cancer and represent as much as has been accomplished in syphilis or tuberculosis. Cancer, comparatively, is a barren field for the investment of public and private funds, yet millions of dollars annually is expended on studies of cancer and programs for prevention of cancer.

The untreated or poorly treated diabetic patient is not only a candidate for diabetic coma but is also predisposed to tuberculosis, to all other infections and to degenerative disorders of all kinds. As a result invalidism overtakes him, usually early, and his life soon is ended. But with proper management these hazards are greatly diminished or prevented, and a vigorous, effective man or woman is preserved. The chief requirement for good results is precise knowledge by the patient of what he needs to do. Today diabetic patients, trained in centers where special attention is paid to diabetes, who have had diabetes fifteen years or more are numbered in the thousands. And of those who received their training in the George F. Baker Clinic, about 900 have attained a *normal* life expectancy. Moreover, the diabetic physicians who have been patients in that clinic have exhibited a death rate lower than that of the other patients, affording the best example of the value of knowledge of the disease by the patient.

What is needed to extend these advantages to the diabetic population at large is more centers for training patients; this, and also much more interest in diabetes on the part of physicians and public health agencies. Diabetes is not a disease requiring a specialist for its management; but it does demand more painstaking attention than many physicians are willing to devote in order adequately to train the patients. These comments are provoked by the illuminating pamphlet, "Advances in the Treatment of Diabetes," issued by the Metropolitan Life Insurance Company and the George F. Baker Clinic.[65] The charts and accompanying comment present a "statistical and clinical epitome of diabetes today." The statement needs amplifying, however. It ought to be followed by the clause "among trained diabetic patients." The charts are part of those that were exhibited at the 1938 meeting of the American Medical Association.

Life tables constructed by Dublin and Marks for diabetic patients treated by Joslin [66] and traced to 1929 reveal dramatically the strides toward normality that well trained diabetic patients have made. The tabulations were constructed by the methods customary in reviewing survivorship experience in insurance investigations. One of the tables is reproduced here. In it the figures for expectation of life by periods (Naunyn, Allen and Banting) of Joslin's patients are compared with the data for the general population of the "original registration states." Appreciable gains are apparent for every age and for both sexes. They are most marked, as was to be expected, in children. A 10 year old diabetic boy of the Naunyn era had an expectancy of only one year, compared with a normal expectancy of fifty-one years, but in the second part of the Banting period the expectancy reached thirty-three and one-fifth years.

Survival figures for patients seen after 1929 in the George F. Baker Clinic undoubtedly will reveal still greater progress, but it is not to be supposed that this represents the general situation. Comparable statistics are nowhere available, but other results probably are much less encouraging, as is illustrated by the shocking mortalities (table 2) reported from abroad and cited by von Ángyán and his associates.[67] Also Kestermann and Schuwicht [68] commented recently that in spite of

65. This pamphlet is obtainable on request from either of the institutions named.

66. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: VI. Mortality and Longevity of Diabetics, Am. J. M. Sc. **195**:596-608 (May) 1938.

67. von Ángyán, J.; Donhoffer, S., and Donhoffer-Mittag, M.: Zur Prognose des Diabetes, Ztschr. f. klin. Med. **133**:466-473, 1938.

68. Kestermann, E., and Schuwicht, E.: Die Lebensschicksale unserer in der letzten 10 Jahren behandelten Diabetiker, Ztschr. f. klin. Med. **133**:458-465, 1938.

insulin the length of life and the duration of the disease for diabetic patients who have died are not appreciably better than in the pre-insulin era, averaging not over six or seven years.

HEMOCHROMATOSIS

Mention must be made belatedly of the excellent monograph on hemochromatosis published in 1935 by Sheldon.[69] The study was based on an intensive search of the literature and the compilation therefrom of data on 311 cases which could be accepted as genuine. The disease

TABLE 1.—*Comparison of Expectation of Life of Diabetic Patients and Persons in the General Population (Joslin, Dublin and Marks [66])*

	Expectation of Life (Years)							
Sex; Age	Diabetic Patients, Naunyn Era	General Population, 1910	Diabetic Patients, Allen Era	General Population, 1919-1920	Diabetic Patients, Banting Era, First Part	General Population, 1919-1920	Diabetic Patients, Banting Era, Second Part	General Population, 1929-1931
Males								
10.....	1.1	51.3	2.8	52.8	10.8	52.8	33.2	54.5
30.....	4.5	34.9	6.5	36.5	16.3	36.5	23.1	36.9
50.....	8.0	20.4	8.6	21.4	11.2	21.4	12.9	20.8
Females								
10.....	1.5	53.6	2.4	53.8	17.8	53.8	30.2	57.1
30.....	3.7	37.0	6.0	37.6	17.4	37.6	22.4	39.3
50.....	8.0	21.7	10.5	22.3	13.4	22.3	13.6	22.7

TABLE 2.—*Mortality Statistics Reported by von Ángyán and His Associates* [67]

		Number of Cases	Deaths, Percentage
Reinwein and Markert	1924-1930	184	38
Grafe	1924-1930	130	43
Henkel	1924-1931	1,082	44
Meythaler and Jakobi	1924-1931	225	40
Büttner	1924-1931	221	48
v. Ángyán and associates	1926-1936	532	26

is rare, but not so rare as formerly was assumed. Butt and Wilder [70] found that the diagnosis had been made in 30 cases at the Mayo Clinic in a period of fifteen and one-half years; the diagnosis in each instance was supported by microchemical examination of the skin. In a family described by Lawrence,[71] hemochromatosis was found in 2 brothers,

69. Sheldon, J. H.: Haemochromatosis, London, Oxford University Press, 1935.

70. Butt, H. R., and Wilder, R. M.: Hemochromatosis: Report of Thirty Cases in Which Diagnosis Was Made During Life, Arch. Path. **26**:262-273 (July) 1938.

71. Lawrence, R. D.: Haemochromatosis and Heredity, Lancet **2**:1055-1056 (Nov. 9) 1935.

with 3 other brothers and the mother showing some signs of the disease. Several other instances of the occurrence of hemochromatosis in brothers were mentioned by Sheldon, and in the series of Butt and Wilder 1 patient had a brother with enlargement of the liver and cyanotic pigmentation. This suggestive evidence of a familial character is consistent with the conclusions reached by Sheldon, Dry [72] and others, that in order to account for the amount of iron retained the onset of the disease must be dated back thirty to fifty years from the time a diagnosis is made. Some inborn error of metabolism seems to be involved which expresses itself in an inability of cells to rid themselves of ferrous compounds no longer useful (Sheldon).

The prognosis in hemochromatosis has been materially improved since the availability of insulin made possible the control of associated diabetes. Lawrence,[73] after reviewing the course of the disease and the duration of life in 12 cases, commented on the improvement as follows:

> No one could yet venture on a prognosis for any particular patient, but it is clear that death can be postponed and activity made normal for many years. As Sheldon suggests, it is likely that a liver death (cholaemia, cirrhosis and ascites) will replace diabetic coma. As regards the liver, I feel that of all forms of cirrhosis—a hard, very large liver—this is probably the best. Here no violent toxic background is present to kill the liver cells, but a slow mechanical cause, the deposition of an iron excess. This gives the liver time to hypertrophy and regenerate enough new cells to maintain full liver function. This can go on adequately for many years, how long no one knows. But no immediately gloomy prognosis is justified if the insulin treatment is successful. I see no reason to tell these patients that they have a fatal disease and think it best, if necessary, to say that their diabetes is complicated by a large liver. The intelligent ones should never hear the words "bronzed diabetes" or "haemochromatosis" when perusal of the older encyclopaedias must be unnecessarily depressing.

GLYCOGENOSIS (VON GIERKE'S DISEASE)

It has been supposed that the upper and middle segments of the thoracic portion of the spinal cord are involved in the glycogenic function of the liver. The same segments provide innervation for other organs (heart, thyroid, parathyroids and adrenals), which not infrequently are involved in glycogenosis. Neuteboom,[74] reporting an atypical case of

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72. Dry, T. J.: Hemachromatosis: Its Relation to the Metabolism to Iron, Proc. Staff Meet., Mayo Clin. **8**:56-59 (Jan. 25) 1933.

73. Lawrence, R. D.: The Prognosis of Haemochromatosis, Lancet **2**:1171-1172 (Nov. 14) 1936.

74. Neuteboom, J. J.: Zur Kenntnis der Glykogenkrankheit (Hepatomegalia glycogenica: Von Gierke-Van Creveld; Cardiomegalia glycogenica: Pompe), Klin. Wchnschr. **17**:1437-1441 (Oct. 8) 1938.

glycogenosis, referred to experimental production of glycogenosis in young rabbits. The implantation of small pieces of platinum between the right articular processes of the fifth and sixth thoracic vertebrae and between the left articular processes of the first and second thoracic vertebrae was followed in 1 animal by the development of an atypical form of glycogenosis, almost exactly like that of the clinical case described. In another animal, injury by a carefully directed blow to the dorsal processes of the second and sixth thoracic vertebrae diminished the sensitivity of the animal to epinephrine and increased the acetone content of the blood and the glycogen content of the liver. The observation is suggestive and warrants further study.

DIABETES INSIPIDUS

Von Hann has been given credit by Findley [75] for the first suggestion that diabetes insipidus cannot occur unless functioning tissue of the anterior lobe of the pituitary is present. It was based on the astute observation, in autopsies of patients, that lesions destructive of the pituitary were associated with diabetes only when functioning tissue of the anterior lobe was spared. Confirmatory experimental studies by others followed. Thus a state of normal water balance seems in part to depend on a balance between the diuretic property of the secretions of the anterior lobe and the antidiuretic action of the posterior lobe of the pituitary. In addition, it has been established experimentally that extracts of the anterior lobe which normally provoke transient diuresis fail to do so in thyroidectomized animals and that the polyuria which follows hypothalamic puncture is greatly diminished by thyroidectomy. On these and other observations is based the current "Hann-Richter-Ranson hypothesis" [75] that the thyrotropic principle of the anterior lobe of the pituitary has diuretic activity and that diabetes insipidus depends on hypopitressinemia in the presence of this diuretic principle of the anterior lobe.

Partly on the basis of this hypothesis and also because of suggestions that the thyroid, perhaps independently, exerts diuretic activity (the well known occasional diuretic efficiency of thyroid and an isolated clinical observation by Strauss [76] of recovery from diabetes insipidus following the onset of spontaneous myxedema), Findley resorted to total ablation of the thyroid in a case of diabetes insipidus. The results were not sufficiently good to lead him to recommend the procedure. The reduction in the volume of urine was no greater than that which could be obtained with a low salt diet; nevertheless, the operation definitely

75. Findley, T., Jr.: Thyroid-Pituitary Relationship in Diabetes Insipidus, Ann. Int. Med. **11**:701-713 (Nov.) 1937.

76. Strauss, L., cited by Findley.[75]

increased the patient's reactivity to administered pitressin and diminished his diuretic response to sodium chloride.

Reference also has been made by Findley to a report by McConnell [77] of striking amelioration of diabetes insipidus in a woman after removal of a thyroid adenoma. The fact that in her case polyuria was said to be uninfluenced by solution of posterior pituitary in any form suggested to Findley that McConnell's observations ought to be repeated on pitressin-resistant patients. Cutler's [78] results with thyroidectomy in diabetes insipidus apparently were not striking.

OBESITY

Personal clinical experience has led us to believe that a good many cases of obesity which commonly have been attributed to glandular disturbances are due in reality to lesions of the central nervous system.[79] Gill,[80] of the Middlesex Hospital, London, in a contribution to the collected papers dedicated to Hagedorn, and Evans,[81] of King's College, London, have contributed recent reports of a number of cases of obesity related chronologically to acute diseases involving the brain. These reports supplement similar contributions of others to whom the authors have referred, such as those of Hall [82] (1924) and von Economo [83] (1931), who described obesity following encephalitis lethargica; Raab [84] (1931), who found cases in which obesity was related to postvaccinal encephalitis, and Gamna [85] (1931), Coburn [86] (1931) and Moncrieff [87] (1932), who commented on its occurrence after rheumatic chorea. Moncrieff's patients had a feminine type of fat deposit. A case of Gamna's was described as an example of the adiposogenital syndrome, and in 1 of Evans' cases the diagnosis previously had been pituitary obesity. Evans has pointed out that the growth of pubic hair in these cases suggests that hypopituitarism is not the active factor.

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77. McConnell, A. A., cited by Findley.[75]

78. Cutler, E. C., cited by Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937, p. 89.

79. Wilder, R. M.: Regulation of the Weight of the Body, Internat. Clin. **1**:30-41 (March) 1932.

80. Gill, A. M.: Unclassified Types of Obesity, Acta med. Scandinav. (supp.) **90**:257-268, 1938.

81. Evans, P. R.: Obesity Following Chorea, Brit. J. Child. Dis. **34**:179-186 (July-Sept.) 1938.

82. Hall, cited by Gill.[80]

83. von Economo, cited by Gill.[80]

84. Raab, cited by Gill.[80]

85. Gamna, cited by Gill.[80]

86. Coburn, cited by Gill.[80]

87. Moncrieff, cited by Gill.[80]

Evans followed 27 patients with chorea; 2 patients were obese and 4 were gaining more rapidly than normal. The obesity began as the attacks of chorea were subsiding—after the first attack in 3 cases, after the second in 1 and after the third in 2. The chorea probably was rheumatic. In 2 cases it was associated with carditis, in 1 with polyarthritis and in others with rheumatic manifestations.

The cause of rheumatic chorea is uncertain, but encephalitis has been found in cases of acute chorea by Poynton and Holmes,[88] and the probability is entertained that obesity consequent to this disease is due to a lesion or lesions in the suprapituitary region of the diencephalon rather than in the pituitary. The treatment of obesity of the cerebral type, in our experience, is dietetic. If rigid control can be maintained the loss of weight can be predicted from the difference between the intake and the estimated total caloric requirement. The difficulty is with the appetite, which often is so grossly abnormal that the patient, like the diabetic patient of the era before insulin, is unable to resist the temptation to break his diet. This makes it extraordinarily difficult to secure his cooperation and to keep it long enough to accomplish all that is desired.

Since 1933 we have employed the very low caloric diet recommended for reduction of obesity by Evans and Strang.[89] Evans[90] now has reviewed his own results with the diet. Ours, with the method modified slightly to provide a more liberal supply of vitamins and minerals, have been very satisfactory.

GOUT

Talbott and Coombs,[91] at the annual meeting of the American Society for Clinical Investigation, reported on a study of values for uric acid in the serum in 68 nonaffected blood relatives of 16 patients with gout. All of these relatives were considered healthy, in none was a past history of acute arthritis obtained and all showed normal roentgenograms of the joints. Yet in 14 of these persons (21 per cent) the uric acid content of the blood serum was greater than the value which Talbott and his associates consider to be the upper limit for normal persons. Several of the persons with an elevated uric acid value were less than 30 years of age, which leads to the supposition that the metabolic abnormality begins at or shortly after birth and that it may exist throughout life without

88. Poynton, F. J., and Holmes, G., cited by Evans.[81]

89. Evans, F. A., and Strang, J. M.: The Treatment of Obesity with Low Caloric Diets, J. A. M. A. **97**:1063-1068 (Oct. 10) 1931.

90. Evans, F. A.: Treatment of Obesity with Low-Calory Diets: Report of One Hundred and Twenty-One Additional Cases, Tr. A. Am. Physicians **53**: 352-355, 1938.

91. Talbott, J. H., and Coombs, F. S.: The Concentration of Serum Uric Acid in Nonaffected Members of Gouty Families, J. Clin. Investigation **17**:508 (July) 1938.

other symptoms. The data lend support to the hypothesis that gout is a familial disease and that one manifestation of it (elevation of the uric acid content of the serum) is subject to hereditary transmission.

The contention of Talbott that analysis for uric acid of *serum* (derived from blood allowed to clot under oil) furnishes more valid data than the customary procedure, in which whole blood is analyzed, is supported by additional data obtained in his laboratory and clinic by Jacobson.[92] In 177 examinations of 21 patients with gout the values ranged from 5.2 to 14.8 mg. per hundred cubic centimeters of *serum*, with values exceeding 6.0 mg. in 98 per cent. For 97 of 100 nongouty persons the values were below 6.0 mg. This is the best evidence of the diagnostic reliability of the value for uric acid yet presented; however, the number of patients examined was small, and the experience of Hench,[93] who has seen annually from 200 to 250 patients, nearly half of them with tophaceous gout, is not corroborative. Jacobson found that high serum values for uric acid were little influenced by a purine-free diet, which also is contrary to the experience of Hench and Slocumb.[94] It is important to emphasize that values for uric acid obtained for blood serum are consistently higher by 1 or 2 mg. than those for whole blood and that the value of 6 mg. per hundred cubic centimeters, set by Talbott and Jacobson, represents about 4.5 mg. for whole blood. Also, until more evidence is presented it will continue to be unjustifiable to base a negative diagnosis of gout on values for uric acid of 4.5 mg. for whole blood or 6 mg. for blood serum. The day is long past when all arthritis went by the name of gout; today the large majority of mistakes in the diagnosis of gout, as Hench[95] repeatedly has emphasized, are failures to recognize gout when gout exists. The fault, he thinks, lies less with the individual physician than with the contemporary American medical thought, which has led physicians to believe that gout is either an extinct or a rare disease. In 40 per cent or more of the cases in which gout is not recognized it is tophaceous. In the others the diagnosis must be stated as "presumptive gout" or "pretophaceous gout," although in many of these cases deeply placed tophi probably escape detection. The report of such a case, in which, incidentally, the uric acid value of the blood serum varied, with the medication given, from 3.8 to 7.14 mg. per hundred cubic centimeters, was made

92. Jacobson, B. M.: Uric Acid in the Serum of Gouty and Nongouty Individuals: Its Determination by Folin's Recent Method and Its Significance in the Diagnosis of Gout, Ann. Int. Med. **11**:1277-1295 (Jan.) 1938.

93. Hench, P. S.: Personal communication to the authors.

94. Hench, P. S., and Slocumb, C. H.: Personal communication to the authors.

95. Hench, P. S.: The Diagnosis of Gout and Gouty Arthritis, J. Lab. & Clin. Med. **22**:48-53 (Oct.) 1936.

by Rutledge and Bedard.[96] In the discussion of this case the following criteria for the recognition of gout, as previously emphasized by Hench,[97] were given detailed consideration:

1. Relatively trivial trauma may provoke an attack of gout the severity of which is out of proportion to the trauma.

2. The dietary indiscretions (food, drink) of holidays, Thanksgiving, Christmas, New Year's Day, the Passover, a birthday and lodge-nights, frequently provoke attacks.

3. A useful maxim is "acute postoperative arthritis occurring within the first six days after an operation is generally gout."

4. The trauma, exposure and the dietary excesses of fishing, hunting and vacation trips are common incitants.

5. An acute attack of gouty arthritis frequently may be precipitated in the course of treatment of gout-susceptible patients for coincident disease; namely, by liver therapy for pernicious anemia, by a ketogenic diet for bacilluria, by salyrgan or other diuretics given for dropsy, by ergotamine tartrate (gynergen) administered for migraine, or rarely by insulin for diabetes.

6. A gouty patient with coincident polycythemia or leukemia is particularly prone to marked activity of his gout.

7. About 98 per cent of patients who have gout are men.

8. The first attack of gout occurs most frequently in patients who are thirty-five years or more of age. Gouty arthritis is the most common form of acute arthritis to affect men aged more than forty years and gout should be thought of first when attacks of arthritis appear in a man of this age if gonorrhea and acute trauma have been excluded.

9. The incidence of attacks of gouty arthritis is greatest in spring and fall although they may occur in any month.

10. While an attack may come on at any time during the day or night, it is especially prone to occur between 2 and 7 a. m.

11. The speed of onset and development of an attack are usually rapid. In no other form of arthritis does maximal disability develop as rapidly as in gout. The maximal pain and swelling always are reached within thirty-six hours of the onset of any attack.

12. The pain of gout may be moderate or severe; it is often "the worst ever" experienced by the victim.

13. From one to two or more joints are involved. The joints of the great toes are usually involved, those of the torso almost never. Podagra or involvement of the big toes is not a sine qua non of gouty arthritis. However, as Hench has noted elsewhere, podagra is present in approximately 60 per cent of attacks.

14. When the great toes are involved the maximal tenderness is generally on the mesial aspect of the metatarsophalangeal joint.

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96. Rutledge, D. I., and Bedard, R. E.: Criteria for the Diagnosis of Presumptive (Pretophaceous) Gout: Management of an Illustrative Case, Proc. Staff Meet., Mayo Clin. **12**:149-156 (March 10) 1937.

97. Hench, P. S.: The Diagnosis of Gout and Gouty Arthritis, Proc. Staff Meet., Mayo Clin. **11**:476-480 (July 22) 1936.

15. The affected foot is not rather cold and bluish-white as in atrophic arthritis but warm and bluish-red; the skin is often shiny; edema and later desquamation of skin are commonly noted.

16. Attacks are usually of relatively short duration varying from seven to twenty-one days.

17. The tendency to full restitution of articular function is notable and for a long time the remissions are complete.

18. Olecranon bursitis is common in gout.

19. Attacks of renal colic or nephritis not uncommonly develop in cases of gout.

An observation of some interest and possible therapeutic significance in gout was reported by Rosenberg,[98] namely, that large doses of insulin administered in the treatment of schizophrenia (9 observations; 3 patients) caused a marked fall in the concentration of uric acid in the blood. The fall was independent of clinical manifestations and occurred even when hypoglycemia was prevented by repeated administration of sugar (7 additional observations; 6 patients). The degree of depression varied on different days for the same patient as well as with different patients from 6.4 to 68.5 per cent, but in 10 of 16 observations it exceeded 25 per cent.

ALKAPTONURIA, OCHRONOSIS AND TYROSINOSIS

The urine in alkaptonuria contains homogentisic acid, an intermediate metabolite of tyrosine. A related condition was described in 1932 by Medes [99] and named tyrosinosis. In it tyrosine is not metabolized beyond the stage of parahydroxyphenylpyruvic acid. The urine of a patient described by her had reducing properties and also gave a positive Millon reaction. A search for other cases was made without success by Blatherwick.[100] His results revealed the extreme rarity of the condition, since he found not 1 instance in 26,000 examinations. A typical case of alkaptonuria with ochronosis was reported recently by Seaborn.[101] The patient was a man 70 years of age, with a history of urine which had stained his clothing from childhood and of recent arthritic pains and stiffness in many joints. The cartilages of the nose and ears and those of the knuckles were dark. Specimens of urine of 135 descendants in the direct line and 71 descendants of cousins of the patient were examined

98. Rosenberg, E. F.: Effect of Insulin on the Concentration of Uric Acid in the Blood, J. Clin. Investigation **17**:233-235 (May) 1938.

99. Medes, G.: A New Error of Tyrosine Metabolism: Tyrosinosis; the Intermediary Metabolism of Tyrosine and Phenylalanine, Biochem. J. **26**:917-940, 1932.

100. Blatherwick, N. R.: Tyrosinosis: A Search for Additional Cases, J. A. M. A. **103**:1933 (Dec. 22) 1934.

101. Seaborn, E.: A Case of Ochronosis, J. A. M. A. **110**:576-577 (Feb. 19) 1938.

at the Institute of Public Health of London, Canada, and in no other specimen than that of the patient was homogentisic acid found. The case is of special interest because of the long history obtained and the number of relatives examined.

BENCE JONES PROTEINURIA

The subject of Bence Jones proteinuria was given attention in this journal by Meyler,[102] who reported detecting Bence Jones protein regularly in normal calf bone marrow, as well as in the pus of abscesses or empyema and in the leukocytes of leukemic blood. The differences in the degree of proteinuria in cases of multiple myeloma as compared with that in leukemia and empyema were attributed to production of the protein in myeloma at a rate greater than the rate at which it normally is metabolized.

ACIDOSIS AND ALKALOSIS

The subject of acid-base balance, although allotted to the section on diseases of metabolism in the textbooks of medicine, involves so many fields of medicine that it never has been possible in this annual review of diseases of metabolism to give it the broad consideration it should receive. This year, however, reference can be made to a valuable general review of the subject by Sendroy.[103] The article covers points of importance and interest that have developed since the publication of the monograph by Peters.[104] In the article, incidental reference is made to the advocacy by Korányi and Szent-Györgyi [105] of succinic acid to combat ketosis in diabetic acidosis. Confirmation of their work has not to our knowledge appeared, but the important positions in medicine and biochemistry which these investigators occupy undoubtedly will lead others to consider their suggestion. Krebs,[106] on purely theoretic grounds, has suggested that citric acid should be more effective.

II. NUTRITION

By Dr. Wilbur

Advances in nutrition during the past year which may be of particular interest to clinicians have had to do chiefly with the vitamins. Information on this subject is being added so rapidly that it is impossible for

102. Meyler, L.: Bence-Jones' Proteinuria, Arch. Int. Med. **57**:708-713 (April) 1936.

103. Sendroy, J., Jr.: Acid-Base Metabolism, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1938, vol. 7, pp. 231-252.

104. Peters, J. P.: Body Water, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

105. Korányi, A., and von Szent-Györgyi, A.: Ueber die Bernsteinsäurebehandlung diabetischer Azidose, Deutsche med. Wchnschr. **2**:1029-1033 (July 2) 1937.

106. Krebs, H. A., cited by Sendroy.[103]

any one individual to keep in touch with the progress that is being made in this field of nutrition.

The discovery during recent months of the marked therapeutic effect of nicotinic acid in cases of pellagra has been an event of outstanding interest to clinicians. Of almost equal interest have been advances made in various biologic and chemical procedures devised for the detection of vitamin deficiency states of mild and "preclinical" character. Much of the information which is now available regarding these problems and those having to do with the chemistry, physiology, pathology and other clinical phases of the vitamins has been reviewed in a series of articles published during the year in *The Journal of the American Medical Association.*

VITAMIN A

Chemistry and Physiology.—Little information of value to clinicians has been added to the knowledge of the chemistry of vitamin A in the past year. The relation of this substance to its precursor carotene, the yellow pigment of plants, has been amply confirmed, as has the fact that conversion of carotene to vitamin A occurs in the liver. It has been suggested that this conversion occurs by means of an enzyme which has been called carotenase. In a recent review of the chemistry of vitamin A, Palmer [107] pointed out that this vitamin is the only one so far discovered which is a product solely of animal metabolism from precursors which are metabolic products of plants only. There has been some evidence to indicate that vitamin A performs its function in chemical combination with other substances rather than as a free substance. This is attested to by the observations that the vitamin is absorbed as a bile acid compound, transported in the blood and lymph as a fat acid ester and stored in the liver as a similar compound. There also seems to be a close chemical relation between a protein vitamin A compound and the visual purple of the retina.

The indispensability of vitamin A for the normal functioning of epithelial cells has been recognized as the basis for the essential pathologic changes in vitamin A deficiency. Wolbach [108] considers that vitamin A may be a structural material which may be solely concerned in maintaining an apparatus within cells and not in the chemical processes proper for which the apparatus is necessary. If this conclusion proves to be true it seems logical, as Booher [109] has suggested, that the vitamin A

107. Palmer, L. A.: The Chemistry of Vitamin A and Substances Having a Vitamin A Effect, J. A. M. A. **110**:1748-1751 (May 21) 1938.

108. Wolbach, S. B.: Vitamin Deficiency Experimentation as a Research Method in Biology, Science **86**:569-576 (Dec. 24) 1937.

109. Booher, L. E.: Vitamin A Requirements and Practical Recommendation for Vitamin A Intake, J. A. M. A. **110**:1920-1925 (June 4) 1938.

requirement should bear a definite relation to body weight rather than to energy metabolism.

The close chemical and physiologic relation of vitamin A to the pigment visual purple and therefore to the clinical manifestation night blindness has been recognized for several years. Recent observations reported by Hecht and Mandelbaum [110] indicate that just as vitamin A enters into the chemical cycle of the rod cells of the retina, owing to its association with visual purple, so it enters into the chemical cycle of cone cells, and that the sensitive substance of the cone cells, iodopsin or visual violet, is likely a conjugated carotenoid protein.

Vitamin A Requirement of Man.—The daily requirement of vitamin A is still unknown. The uncertainty of the requirement of man for this substance lies in the fact that there is wide variability in minimal and optimal requirements and in absorption, storage, utilization and destruction of the vitamin and that there is not complete agreement as to the standard which should be established as a measure of vitamin A sufficiency. Booher,[109] who has recently reviewed the literature in regard to this problem, concludes that about 1,400 to 2,000 U. S. P. units of vitamin A daily for an adult weighing 70 Kg. suffices for the support of normal visual adaptation. It was suggested that the daily intake of vitamin A per kilogram of body weight of adults required for the prevention of night blindness (20 to 30 U. S. P. units per kilogram) might be nearly a constant for vertebrate animals generally. Allowing a 50 per cent margin of safety for the maintenance of a moderate storage of vitamin A in the body, a total of about 3,000 U. S. P. units of vitamin A daily has been suggested by Booher [109] for the normal adult. Provision of 6,000 to 8,000 U. S. P. units of the vitamin for growing children and of at least 5,000 U. S. P. units for pregnant and lactating women would presumably be adequate. The latter amount would be that contained in 1 quart (1 liter) of fresh whole milk, one egg, 1 ounce (28 Gm.) of cheese, an average serving of a green leafy vegetable and 1 teaspoonful of cod liver oil daily.

Somewhat lower values for the minimal daily requirement of vitamin A were suggested by Edmund and Clemmesen,[111] who studied a group of prisoners by means of dark adaptation tests and concluded that a diet containing 1,370 U. S. P. units daily was adequate to obliterate seasonal oscillations in power of distinction and that therefore this amount is necessary for an adult.

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110. Hecht, S., and Mandelbaum, J.: Rod-Cone Dark Adaptation and Vitamin A, Science **88**:219-221 (Sept. 2) 1938.

111. Edmund, C., and Clemmesen, S.: On Deficiency of A Vitamin and Visual Dysadaptation: II., London, Oxford University Press, 1937, pp. 1-77.

The Effects of Vitamin A Deficiency on Certain Organs.—Clinicians in this country who are interested in deficiency states read much concerning the cutaneous manifestations of vitamin A deficiency but apparently do not commonly recognize them. It has been suggested that the cutaneous lesions are among the earliest if not the earliest clinical manifestation of deficiency of vitamin A. There have been numerous reports of the appearance of such lesions, but most of them have been published from observations made in the Orient or in Africa.

In the past year Youmans and Corlette [112] have recorded observations on 6 patients with cutaneous lesions which were considered to be due to vitamin A deficiency. They observed two types of changes—the first consisting of a gooseflesh or horny type of eruption, similar grossly and histologically to the type reported by Frazier and Hu,[113] and the second a type of lesion which resembled in many but not in all respects the acne pustule, with the exception that pustulation was uncommon. Youmans and Corlette, furthermore, emphasized an important point in diagnosis and therapy, namely, that improvement in the cutaneous lesions is seldom noted in less than four weeks and that in many instances twelve to fourteen weeks is required before the eruptions disappear. If the response to vitamin A therapy is to be used as a diagnostic procedure, it is important to remember that the response is slow, depending as it does on anatomic repair, in contrast to the relief of the night blindness of vitamin A deficiency, in which the response to therapy depends on physiologic changes only and therefore occurs in a matter of hours or a few days.

Keil [114] has also published studies on the cutaneous follicular lesions of vitamin A deficiency and has attempted to establish criteria for distinguishing them from the cutaneous lesions of vitamin C deficiency.

In a review of the influence of vitamin therapy on lesions of the skin Stokes, Beerman and Ingraham [115] have come to the conclusion that high vitamin therapy, as far as it concerns cutaneous inflammatory disease, has a not too highly specific but rather a shotgun quality, concerned mainly with the effect of vitamins on the general constitution and nutrition of patients. They have pointed out that the two nearest

112. Youmans, J. B., and Corlette, M. B.: Specific Dermatoses Due to Vitamin A Deficiency, Am. J. M. Sc. **195**:644-650 (May) 1938.

113. Frazier, C. N., and Hu, C. K.: Cutaneous Lesions Associated with Deficiency of Vitamin A in Man, Arch. Int. Med. **48**:507-514 (Sept.) 1931.

114. Keil, H.: The Follicular Lesions of Vitamine A and C Deficiencies: A Critical Survey, Am. J. Digest. Dis. **5**:40-48 (March) 1938.

115. Stokes, J. H.; Beerman, N., and Ingraham, N. R., Jr.: Carbohydrate and Water Metabolism and the Vitamins in Skin Inflammation (Dermatitis), Am. J. M. Sc. **195**:562-574 (April) 1938.

approaches to a specific use for vitamin therapy are found for vitamin A in keratodermic disturbances and their associated pyogenic infections and in senile vaginitis and pruritis vulvae.

Clausen [116] has presented an excellent review of the pharmacology and therapeutics of vitamin A in a recent article in *The Journal of the American Medical Association.* Some of his conclusions are worthy of repetition here because they summarize information gathered over a period of recent years which should be of considerable interest to clinicians. Clausen has pointed out that the absorption of vitamin A appears to be accomplished by means of a mechanism which includes linkage of the vitamin with fatty acids, probably in the intestinal wall. This normal process is interfered with when bile is excluded from the intestine during infections and in patients with steatorrhea. Nothing is known of the degree of destruction of vitamin A in the gastrointestinal tract. Evidence that antagonism exists between the action of thyroxine and that of vitamin A is suggested by the following observation: In experimental animals the loss of weight due to daily ingestion of thyroxin could be prevented by the administration of vitamin A. Improvement of patients with various types of disease of the thyroid following the use of vitamin A in large amounts has been reported.

Clausen [116] has found that the majority of investigators fail to obtain evidence that a deficiency of vitamin A alone will cause stone in the urinary tract. The influence of moderate vitamin A deficiency on the reproductive organs of the male is unknown, while for the female the characteristic change is in the vaginal mucous membrane, which becomes permanently cornified. There also may be an effect on or through the ovary, but the effect on the hypophysis is unknown.

Anemia is not a regular symptom of vitamin A deficiency, and the use of vitamin A for the treatment of anemia does not rest on a secure foundation. In fact, Clausen [116] concludes that no striking effect of vitamin A deficiency on the cellular elements of the blood has been discovered.

Vitamin A has been sold for some years as the "anti-infectious vitamin," without much justification. On this point Clausen has said:

> The evidence reviewed indicates that severe deficiency of vitamin A lowers resistance to infection in man and that the administration of vitamin A during the course of an infection probably has no beneficial effect on the outcome unless severe deficiency is present. There is evidence that moderate deficiency of vitamin A may also increase the duration or severity of respiratory infections in man; that an adequate intake of vitamin A may lessen the severity and duration of infection in persons moderately deficient. It is also evident that many other factors

116. Clausen, S. W.: The Pharmacology and Therapeutics of Vitamin A, J. A. M. A. **111**:144-154 (July 9) 1938.

are of equal or greater influence on infection, and no justification exists for calling vitamin A "the anti-infective vitamin."

Effect of Vitamin A on Nutritional Well-Being.—While vitamin A in small quantities is indispensable for normal health, there has been much discussion of the possible effect of optimal doses on healthy animals and on man. Sherman and Campbell [117] in their studies of rats have found that the three factors which were increased in greatest ratio when an already adequate diet was modified to constitute a nutritionally better diet were calcium, vitamin A and riboflavin. On the other hand, Lewis and Barenberg [118] sought information on the margin of safety with respect to the vitamin A content of the average diet of infants. To 51 infants they gave a diet which contained approximately one-fourth the vitamin A content of the average diet, and to 53 infants they gave a diet which contained from four to eight times the number of vitamin A units contained in the average diet (the average diet contained 2,100 to 4,700 U. S. P. units of vitamin A, depending on the age of the infant). After an average period of six to eight months a comparison of the nutritional status and incidence of infection in the two groups was made. The results showed that there was no difference between the two groups in either of these respects, which led the authors to conclude that the average diet of infants contains at least four times as many units as the minimum requirement, as judged by the nutritional state of infants and by their reactions to infection.

Diagnostic Procedures for Vitamin A Deficiency.—Eyes: Since the earliest clinical manifestations of vitamin A deficiency have to do with the eyes, it is natural that efforts to make a diagnosis of early vitamin A deficiency would rest in part on efforts to measure by laboratory or other procedures those changes in the eyes which are characteristic of vitamin A deficiency. In general, such methods fall into two groups: the first, examination of epithelial cells scraped from the bulbar conjunctiva and, the other, estimation of the ability of the eyes to adapt themselves to darkness. The former method of examining smears for keratinized cells is believed by Youmans and his associates [119] to be inadequate.

The latter method of examination is based on the well established fact that moderately severe vitamin deficiency is accompanied by an

117. Sherman, H. C., and Campbell, H. L.: Nutritional Well-Being and Length of Life as Influenced by Different Enrichments of an Already Adequate Diet. J. Nutrition **14**:609-620 (Dec.) 1937.

118. Lewis, J. M., and Barenberg, L. H.: The Relationship of Vitamin A to the Health of Infants, J. A. M. A. **110**:1338-1341 (April 23) 1938.

119. Youmans, J. B.; Corlette, M. B.; Corlette, M. G., and Frank, H.: Inadequacy of Conjunctival Smears in Diagnosis of Slight Vitamin A Deficiency in Adults, J. Lab. & Clin. Med. **23**:663-670 (April) 1938.

abnormality of the dark adaptation reaction. Measurements of alterations of dark adaptation have been made in large part in this country by the biophotometric method popularized by Jeans and Zentmire.[120] There has been much discussion of the value of this method as a diagnostic procedure, and in my opinion there is still sufficient evidence to suggest that the test cannot be considered a satisfactory or a reliable method for detecting mild forms of vitamin A deficiency. The extensive studies of Jeghers,[121] noted last year, indicated that the method was of value, and more recently Corlette, Youmans, Frank and Corlette[122] have reported that they have found the method satisfactory for the making of photometric studies of adults. They have proposed an initial recovery reading of 0.70 milli-foot-candle as a tentative value for the normal limit of dark adaptation. Using this criterion they found that 50 per cent of a group of ambulatory adult outpatients had poor dark adaptation, indicating mild vitamin A deficiency. The great majority of these patients improved after treatment with vitamin A.

On the other hand, Snelling,[123] Palmer and Blumberg[124] and more recently Palmer[125] have collected information which they feel casts doubt on the value of the biophotometric test as a means of measuring the vitamin A status of patients. The principal criticisms of the method noted by these workers were that the results are variable and have little consistency for children (Snelling[123]), that considerable improvement in readings, apparently due to the learning factor, resulted from repeated testing of the same children (Palmer and Blumberg[124]) and that in one study the results obtained showed no significant difference in the improvement in biophotometric measurements in a group of children whose diet was supplemented by 18,000 U. S. P. units of vitamin A and a control group whose diet was not supplemented with vitamin A

120. Jeans, P. C., and Zentmire, Z.: A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, J. A. M. A. **102**:892-895 (March 24) 1934. Jeans, P. C.; Blanchard, E., and Zentmire, Z.: Dark Adaptation and Vitamin A, ibid. **108**:451-456 (Feb. 6) 1937.

121. Jeghers, H.: Night Blindness as a Criterion of Vitamin A Deficiency, Ann. Int. Med. **10**:1304-1334 (March) 1937.

122. Corlette, M. B.; Youmans, J. B.; Frank, H., and Corlette, M. G.: Photometric Studies of Visual Adaptation in Relation to Mild Vitamin A Deficiency in Adults, Am. J. M. Sc. **195**:54-65 (Jan.) 1938.

123. Snelling, C. E.: The Biophotometer as a Test for Vitamin A Deficiency, J. Pediat. **13**:506-609 (Oct.) 1938.

124. Palmer, C. E., and Blumberg, H.: The Use of a Dark Adaptation Technique (Biophotometer) in the Measurement of Vitamin A Deficiency in Children, Pub. Health Rep. **52**:1403-1419 (Oct. 8) 1937.

125. Palmer, C. E.: The Dark Adaptation Test for Vitamin A Deficiency, Am. J. Pub. Health **28**:309-315 (March) 1938.

(Palmer [125]). Furthermore, Booher and Williams,[126] as a result of their quantitative studies of the problem, have concluded that, "provided the worker is equipped with suitable means for frequent calibration of the intensity of light emanating from the illuminated central dot of the test screen and from the large diffusing plate used for light adaptation, the biophotometer *may* be adequate for detecting *marked* dysadaptation in adults." [127]

The whole situation has been well summarized by Palmer,[125] who thinks that theoretically it is probable that it should be possible to measure quantitatively the vitamin A nutritional status by means of the dark adaptation tests but that as yet the method is not practicable nor satisfactory.[127a]

While the value of the biophotometric test as a measure of vitamin A deficiency is still on trial, the fact that disturbances in dark adaptation may occur in vitamin A deficiency has received practical application in the prevention of night blindness among those who drive automobiles at night and, according to a recent report by Wise and Shettler,[128] among color matchers in an industrial organization. These observers have found that by giving three capsules of carotene in oil daily to color-matching inspectors, the efficiency of these workers was improved by 75 per cent and there was a decrease in incidence of headaches and of burning and smarting of the eyes.

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126. Booher, L. E., and Williams, D. E.: A Study of the Biophotometer as a Means of Measuring the Vitamin A Status of Human Adults, J. Nutrition **16**: 343-354 (Oct.) 1938.

127. The italics have been inserted by me.

127a. Additional evidence suggesting that measurements of dark adaptation theoretically and practically should be of value in determining the nutritional status of vitamin A of an individual has been presented by Hecht (Hecht, S.: Dark Adaptation and the Diagnosis of Avitaminosis A Nutrition: The Newer Diagnostic Methods, Proceedings of the Round Table on Nutrition and Public Health, New York, Milbank Memorial Fund, 1938, p. 32). His studies indicate that the biophotometric test as it ordinarily is performed may not be an accurate measure of dark adaptation because of certain technical defects in the method. He is of the opinion that factors such as the intensity and duration of the preadaptation light, and the area, the retinal location, the color and the duration of the measuring light must be specified for the test to be an adequate one.

An instrument which he and his associates have devised appears to overcome some of the previously stated objections to this test and to satisfy the requirements that have been noted. The results show clearly that cone function is affected by changes in the status of vitamin A just as rod function is affected by them. With this instrument Hecht is able to show an almost immediate rise (within twenty-four hours) in the intensity level of the dark adaptation of healthy persons deprived of vitamin A. In other words, this method seems to be a very sensitive one, and if the findings are verified it may prove to be of great value in the diagnosis of early vitamin A deficiency.

128. Wise and Shettler, cited, Carotene-in-Oil to Ease Eyestrain, Science News, Science (supp.) **87**:11-12 (June 10) 1938.

Studies of the content of carotene and vitamin A in the blood plasma are gradually adding information not only of physiologic but probably also of diagnostic value. Methods of determining the quantity of vitamin A in plasma are not as satisfactory as are methods of determining the content of vitamin C. In a recent critical analysis of methods of assay of vitamin A Munsell [129] pointed out that the blue color reaction with antimony trichloride is no longer considered to have possibilities as the basis of a specific and dependable quantitative method, although it may still be used routinely for certain purposes of control. She is of the opinion that the spectrographic method of analysis holds promise of eventually becoming an accepted technic for quantitative work, although it is now largely in the investigative stage.

A combination of physiologic and chemical methods of assay of vitamin A has been reported by Dann and Evelyn,[130] who have used a photoelectric colorimeter to measure the blue of the antimony trichloride reaction. They believe that the method will be of value because it combines accuracy with convenience and economy and is entirely objective. The method has apparently been used with success by May [131] in determining the vitamin A content of serum.

In recent studies made by Clausen and McCoord [132] the vitamin A content of the blood plasma (or serum) was estimated by the Price-Carr antimony trichloride reaction. They found the mean values in 119 observations on persons without infections and over 2 years of age to be 20.2 U. S. P. units for each hundred cubic centimeters of plasma, with a standard deviation of 10 units. They observed also that infections cause a prompt and considerable fall in the concentration of carotene, xanthophyll and vitamin A in the plasma, owing in part to low intake during infection and in part to fever. A few days after the temperature becomes normal, the vitamin A content of the plasma may rise considerably above normal. They noted also that in Bright's disease the level of plasma may be greatly elevated, probably because the liver fails to store the vitamin. In hypothyroidism, on the other hand, the vitamin A content of the plasma may be low, and successful treatment with thyroid is said to correct the anomaly.

Van Veen and his associates [133] studied the vitamin A content of the blood serum of native prisoners in Batavia who were on a diet

129. Munsell, H. E.: Vitamin A.: Methods of Assay and Sources in Foods, J. A. M. A. **111**:245-252 (July 16) 1938.

130. Dann, W. J., and Evelyn, K. A.: The Determination of Vitamin A with the Photoelectric Colorimeter, J. Biochem. **32**:1008-1017 (June) 1938.

131. May, C., cited by Dann and Evelyn.[130]

132. Clausen, S. W., and McCord, A. B.: The Carotenoids and Vitamin A of the Blood, J. Pediat. **13**:635-650 (Nov.) 1938.

133. van Veen, A. G.; Lanzing, J. C., and Agoes, M.: Providing Prisoners with Vitamin A, Geneesk. tijdschr. v. Nederl.-Indië **77**:3024-3039 (Nov. 30) 1937.

practically free from vitamin A. Nevertheless, the average content of vitamin A in the serum did not differ greatly from that of persons in Europe and other persons in Batavia, because the diet of the Batavian native is high in carotenoid pigments. In other natives of Batavia, namely, in children suffering from xerophthalmia, de Haas and Meulemans [134] found as a rule that the serum contained no vitamin A; occasionally a trace was present. They observed that if the cornea was not perforated, even though temporarily there was no vitamin A in the blood, treatment with a preparation of vitamin A would relieve the disease of the eye.

Therapy with Vitamin A.—There has been no significant change in the treatment of vitamin A deficiency. Concentrates of the vitamin are available principally in the form of concentrated fish liver oils. Carotene is also available as a therapeutic agent. Effective therapeutic doses are in the neighborhood of 10,000 to 70,000 U. S. P. units daily. As yet a satisfactory preparation of the vitamin which may be conveniently administered parenterally is not available. Carotene, cod liver oil and concentrates of vitamin A have been given intramuscularly, but their widespread clinical use is not practical. Reports such as that of Leak [135] on the effect of parenteral administration of vitamin A are based on the use of the vitamin in a form specially prepared for this method of administration.

There is little to fear in the way of toxic effect from therapeutic use of vitamin A. Further substantiation of this fact is provided in the work of Vedder and Rosenberg,[136] who used a preparation of jewfish liver oil on rats and found that if the vitamin is ever toxic it is in doses in excess of 100,000 U. S. P. units daily for 50 Gm. rats. Similarly, the fear that cod liver oil in average therapeutic doses is toxic is denied by the observation of Burack and Zimmerman,[137] who found that in ordinary therapeutic doses this substance is not injurious.

THE VITAMIN B COMPLEX

While the individual components of the vitamin B complex frequently are considered as one group, they differ widely chemically and

134. de Haas, J. H., and Meulemans, O.: Vitamin A and Carotinoids in Blood: Deficiencies in Children Suffering from Xerophthalmia, Lancet **1**:1110-1111 (May 14) 1938.

135. Leak, W. N.: Clinical Observations on the Effect of the Parenteral Administration of Vitamins A and D, Lancet **1**:599-603 (March 12) 1938.

136. Vedder, E. B., and Rosenberg, C.: Concerning the Toxicity of Vitamin A, J. Nutrition **16**:57-68 (July) 1938.

137. Burack, E., and Zimmerman, H. M.: Studies on the Alleged Toxic Action of Cod Liver Oil, J. Nutrition **14**:535-551 (Dec.) 1937.

physiologically and in their clinical behavior. In the past year two substances which have been obtained in crystalline form have been identified definitely as components of the complex; these are nicotinic acid and vitamin B_6.

The components originally were separated into groups because of their ability to promote growth of rats or to cure or prevent polyneuritis or beriberi. Subsequently it was shown that the substance or substances which were necessary for growth were thermostable, and to them was given the name vitamin B_2 or G. The antineuritic element was shown to be thermolabile and is now know as vitamin B_1, thiamin or aneurin. More recent studies have demonstrated other thermolabile factors. Williams and Spies [138] have listed the thermolabile factors as follows:

1. Vitamin B_1, thiamin or aneurin.
2. Vitamin B_3, necessary in addition to 1 for the weight maintenance of pigeons.
3. Vitamin B_4, regarded as necessary for growth of rats and to protect them against a paralysis.
4. W factor, the alcohol ether precipitate from liver extract. Protein in nature.
5. Antigizzard erosion factor, perhaps identical with or related to B_3.

Even more confusing to chemists and clinicians than the thermolabile components of the vitamin B complex are the members of the thermostable group. As Williams and Spies [138] have emphasized, the diversity of results reported by various investigators who have tried to classify these components appears to be due to dependence on a variety of raw materials and on the use of various fractionation methods as well as on differences in the species of animals chosen for test purposes. These authors have listed the components of the thermostable group as follows:

Adsorbed

1. Riboflavin, rat growth promoting, cataract preventing, turkey dermatitis preventing.
2. Nicotinic acid, black tongue and pellagra curative (perhaps not the sole pellagra vitamin).
3. B_5, ill defined thermostable pigeon weight factor.
4. B_6, rat growth promoting, anti-acrodynia factor isolated but not identified, also called factor 1.

Unadsorbed (Filtrate Factors or Factor 2)

1. Chick dermatitis factor.
2. Gray hair preventing factor.

138. Williams, R. R., and Spies, T. D.: Vitamin B_1 and Its Use in Medicine, New York, The Macmillan Company, 1938.

Unclassified Factors Possibly Associated with the B Complex.

1. Extrinsic factor.
2. Anti-egg white injury factor.
3. Antianemic factor.
4. Choline factor.

Of these factors in the B complex, thiamin and nicotinic acid have been found to be of great therapeutic importance in man, while riboflavin and vitamin B_6, which have been identified and obtained in crystalline form, have not been definitely identified as agents of therapeutic importance. The other possible components noted in this list are as yet not identified, and there is considerable discussion as to their importance in the nutrition of man and, in fact, as to their existence.

Vitamin B_1 (Thiamin Chloride).—Chemistry and Physiology: The chemistry of thiamin is well known, and details of its properties may be found in the book by Williams and Spies [138] or in an article by Williams.[139] Apparently the substance has an important role in the enzyme system, resulting in the oxidation of carbohydrates and particularly of pyruvic and lactic acid, and it participates in the function of several other enzyme systems as well. It is likely that the vitamin or a molecule of which the vitamin is a part is coupled with a protein carrier and that either the combination exhibits enzymatic activity or in certain instances the vitamin may be a member of a system which is necessary for the activation of an important enzyme. Indeed, as Williams [140] has pointed out, thiamin is the most conspicuous example of those vitamins which possess a universal or nearly universal function in living cells.

A further suggestion that thiamin may play a role in fat metabolism has been given by Gavin and McHenry,[141] who found that in rats the substance causes an accumulation of dietary or synthesized fat in the liver. On the contrary, vitamin B_6 promotes storage of such fat in the fat depots.

Requirement of Vitamin B_1: Little information has been added to estimates of the requirement of vitamin B_1 noted in the review of last year.[142] A daily intake of 1 or 2 mg. in food by adults apparently satisfies the requirement of man for this substance. Cowgill [143] has

139. Williams, R. R.: The Chemistry of Thiamin (Vitamin B_1), J. A. M. A. **110**:727-732 (March 5) 1938.

140. Williams, R. R.: The Chemistry and Biological Significance of Thiamin, Science **87**:559-563 (June 24) 1938.

141. Gavin, E. G., and McHenry, E. W.: The Relation of the Vitamin B Complex to Fat Metabolism, J. Nutrition (supp.) **15**:10 (June) 1938.

142. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition, Arch. Int. Med. **61**:297-365 (Feb.) 1938.

143. Cowgill, G. R.: Human Requirements for Vitamin B_1, J. A. M. A. **111**: 1009-1016 (Sept. 10) 1938.

pointed out that the requirement for vitamin B_1 may be influenced by such clinical factors as the level of energy metabolism, which is affected principally by fever and hyperthyroidism, and by the loss of the vitamin through excretory channels, such as occurs with diarrhea and diuresis. Estimations of the vitamin requirement of an individual have been accomplished in the past by such means as Cowgill's formula, the calculation being based on the weight of the individual and on the vitamin-calory ratio of his diet. Cowgill [143] further has pointed out that estimates derived from his formula pertain to the minimum or beriberi-preventing level and that the optimal level is undoubtedly much higher. Williams and Spies,[138] after a careful analysis of the situation, feel that a "thiamin-non-fat-calorie ratio" is the best tentative index of adequacy for protection of the average individual that can be offered at present.

Knott and Schlutz [144] have reported that the requirement of infants for vitamin B_1 is higher for each unit of body weight than that of older children. The determinations in their study were made by retention studies, and the authors noted that in the case of infants the vitamin is almost completely absorbed, as contrasted with the findings for older children, who excrete considerable quantities in the feces.

Adequacy of Vitamin B_1 in the Average Diet: A problem of great interest and importance is that of the adequacy of the vitamin B_1 content of the average diet. In the work of Baker, Wright and Drummond,[145] noted in the review of last year, evidence was presented to show that the best fed members of the population in Great Britain today, while receiving twice as much vitamin B_1 as is received by persons with a low income, consume less vitamin B_1 than did the parish poor of the eighteenth and early nineteenth centuries. More recently Jolliffe [146] has published studies of the vitamin B_1 content of the average American diet. He has noted that, as in the case of the British, Americans in 1840 consumed about three times the amount of vitamin B_1 that is obtained by the average American today. Jolliffe is of the opinion that the margin of safety as regards the vitamin B_1 content of the American diet varies from 20 to 80 per cent and that a large proportion of the population, particularly those spending less than $2 per week per capita for food, subsist on diets of borderline adequacy of vitamin B_1. The consequence is, as Strauss [147] has stated, that beriberi is really endemic in this country.

144. Knott, E., and Schlutz, F. W.: The Vitamin B Requirement of Infants, J. Nutrition (supp.) **15**:16-17 (June) 1938.

145. Baker, A. Z.; Wright, N. D., and Drummond, J. C., cited by Jolliffe.[146]

146. Jolliffe, N.: A Clinical Evaluation of the Adequacy of Vitamin B_1 in the American Diet, Internat. Clin. **4**:46-66 (Dec.) 1938.

147. Strauss, M. B.: The Therapeutic Use of Vitamin B_1 in the Polyneuritis and Cardiovascular Conditions, J. A. M. A. **110**:953-956 (March 26) 1938.

Role of Vitamin B in Resistance: Studies of deficiency diseases produced in animals by inadequate feedings of vitamins have revealed that infections of various types are commonly prominent features of the resulting deficiency states. For a time vitamin A was presumed to be the "anti-infective vitamin," but more recently vitamin C has taken its place, because of its apparently important role in the processes of immunity. Not much stress has been placed on a possible role for vitamin B in resistance, but within the past year Perla [148] has reviewed much of the evidence that is available on this subject. He has considered the components of the vitamin B complex as a group, with the exception that in some of the reports that he has reviewed the results were considered in terms of vitamin B_1 alone. He has noted that scattered evidence reported in the literature indicates an increase in frequency of spontaneous infections in animals and in man fed diets deficient in vitamin B. Apparently the role of vitamin B in natural resistance is indirect and is secondary to its importance in cellular metabolism and in the processes of oxidation. A definition of the relative importance of the various components of this vitamin in resistance is not possible at present.

Methods of Determining Vitamin B_1: During the past year some advance has been made in the determination of vitamin B_1 and in assays of the content of the vitamin in various body fluids and excretions. Previously most studies involving assay of vitamin B_1 have been accomplished by means of biologic methods, but in recent years chemical methods have been developed. An excellent summary of these biologic and chemical methods of assay has been given by Munsell.[149]

The most widely studied method of chemical assay of thiamin is the thiochrome method. By using this method improved by details in technic, Ritsert [150] expressed the opinion that he could determine amounts of thiamin as small as approximately 1 international unit per hundred cubic centimeters of urine. He suggested that 30 to 150 international units is excreted in the urine daily. This contrasts with the findings of Harris and Leong,[151] who used the bradycardia method, which is a biologic method. They found that the daily output is from 12 to 35 international units.

148. Perla, D.: Role of Vitamin B in Resistance, Arch. Path. **25**:539-568 (April); 694-729 (May) 1938.

149. Munsell, H. E.: Vitamin B_1, Methods of Assay and Food Sources, J. A. M. A. **111**:927-934 (Sept. 3) 1938.

150. Ritsert, K.: Zur Aneurinbestimmung im Harn nach der Jansenschen Thiochrommethode, Deutsche med. Wchnschr. **64**:481-484 (April 1) 1938.

151. Harris, L. J., and Leong, P. C.: Vitamins in Human Nutrition: The Excretion of Vitamin B_1 in Human Urine and Its Dependence on the Dietary Intake, Lancet **1**:886-894 (April 18) 1936.

In a more recent study Rowlands and Wilkinson,[152] using the biologic method of Schopfer's phycomyces test, have reported their studies of the clinical significance and estimation of vitamin B_1 in the blood. They are of the opinion that the method can be developed as a reasonable test for vitamin B_1 nutrition and that it appears to be the best method at present available for dealing with the small quantities of vitamin B_1 in the blood. The test is too laborious and exacting in technic to serve as an ordinary routine laboratory method. They have placed the range for the vitamin B_1 content of the blood of 8 normal subjects at 6.5 to 16.5 micrograms per hundred cubic centimeters. This compares favorably with the figures of Meiklejohn,[153] previously reported. Gross deficiencies in the vitamin B_1 content of the blood were present in cases of alcoholic neuritis, nutritional neuritis, scurvy and malnutrition, and partial deficiency was present in simple anemia due to achlorhydria. Sinclair [154] has objected to the results reported by Rowlands and Wilkinson,[152] because he believes that they are statistically worthless and that the method of analysis which was used does not give quantitative estimates of the vitamin B_1 content of the blood.

As Williams and Spies [138] have stated, "Chemical methods of assay are promising but as yet insufficiently developed for the study of foods; those involving growth of microorganisms require more vigorous proof of specificity before they can be trusted for general purposes."

The Effect of Vitamin B_1 Deficiency; Diagnosis and Treatment: 1. Nervous system. It is generally agreed that the peripheral neuritis of beriberi is caused by deficiency of this vitamin. The evidence for this has been tabulated by Williams and Spies [138] and by Jolliffe.[146] The frequency with which the symptoms of polyneuritis of beriberi occur in the general population is unknown. Jolliffe and Frank [155] found that 61.6 per cent of 1,000 men admitted consecutively to the ward for alcoholic addicts at Bellevue Hospital in the fall of 1935 had polyneuritis. The condition is observed not uncommonly in women during gestation and in persons with chronic gastrointestinal disorders, diabetes mellitus and hyperthyroidism.

Shattuck [156] has recently reviewed reports of cases of Landry's paralysis or syndrome and has reported that the features of the original cases reported by Landry are consistent with a diagnosis of beriberi.

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152. Rowlands, E. N., and Wilkinson, J. F.: The Clinical Significance and Estimation of Blood Vitamin B_1, Brit. M. J. **2**:878-883 (Oct. 29) 1938.

153. Meiklejohn, A. P.: The Estimation of Vitamin B_1 in Blood by a Modification of Schopfer's Test, Biochem. J. **31**:1441-1451 (Sept.) 1937.

154. Sinclair, H. M.: Estimation of Blood Vitamin B_1, Brit. M. J. **2**:1060 (Nov. 19) 1938.

155. Jolliffe, N., and Frank, P., cited by Jolliffe.[146]

156. Shattuck, G. C.: "Landry's Paralysis" in Relation to Vitamin B_1 Deficiency, Internat. Clin. **3**:24-29 (Sept.) 1938.

He feels that a noteworthy proportion of conditions so diagnosed are due to deficiency of vitamin B_1.

The early diagnosis of the polyneuritis of beriberi is of great importance. Goodhart and Jolliffe [157] have used the following criteria to designate mild involvement: "The signs must be limited to the lower extremities with the knee jerks preserved and with no obvious muscle atrophy or foot drop; the patient must show absent ankle jerks plus some demonstrable sensory changes such as muscle tenderness, skin hyperesthesia in a peripheral nerve distribution and impairment of vibratory or position sense." Vedder [158] has described the following points as of early diagnostic value: 1. Slight pressure over the muscles of the calf causes pain. 2. Patients with beriberi often have areas of anesthesia over the anterior surface of the tibia. 3. Any modification of the patellar reflexes is suspicious. 4. If a patient with beriberi squats on his heels after the Oriental manner of sitting, he may experience pain and an inability to rise without using his hands. The excellent description by Strauss [147] of the early symptoms of polyneuritis of beriberi was noted in last year's review.

The treatment of polyneuritis of beriberi has become highly successful since the introduction of concentrated and crystalline forms of the vitamin. The principal problem in this respect at present is to determine the optimal amount of vitamin B_1 which should be given. As a result of their studies of 17 alcoholic addicts having uncomplicated polyneuritis, Goodhart and Jolliffe [157] feel that improvement in the objective signs of the polyneuritis varies directly with the vitamin B_1 intake up to a point of optimal dosage, which though not yet determined, is definitely more than four times the predicted maintenance dose. Williams and Spies [138] advocated for the adult with polyneuritis a well rounded diet of 4,500 calories, including food of high vitamin B_1 value, supplemented whenever possible by one or several of the following items: dried brewer's yeast (6 ounces [170 Gm.]), wheat germ (6 ounces daily) or crystalline vitamin B_1 (10 mg. twice daily). The crystalline vitamin B_1 may be given parenterally if there is interference with gastrointestinal function. Stern [159] has advocated giving thiamin intrathecally for a variety of neurologic disorders, but there seems to be little advantage in giving it in this way as compared to its administration by the intramuscular or intravenous route.

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157. Goodhart, R., and Jolliffe, N.: Effects of Vitamin B (B_1) Therapy on the Polyneuritis of Alcohol Addicts, J. A. M. A. **110**:414-419 (Feb. 5) 1938.

158. Vedder, E. B.: Beriberi and Epidemic Dropsy, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 4.

159. Stern, E. L.: Intraspinal (Subarachnoid) Injection of Vitamin B_1 for Relief of Intractable Pain, and for Inflammatory and Degenerative Diseases of Central Nervous System: Preliminary Report, Am. J. Surg. **39**:495-511 (March) 1938.

An observation indicating that the acute neuritis of leprosy may be due to vitamin B_1 deficiency was given in the report by Badger and Patrick.[160] They had under their care patients with leprosy who had extremely severe pain and who obtained relief from pain in some cases in as short a time as twenty-four hours. Apparently the results were obtained when the preparation of vitamin B_1 was given parenterally but not when it or yeast was given by mouth.

2. Cardiovascular effects. During the past year little of clinical interest has been added to the knowledge of the cardiovascular symptoms and signs of beriberi noted in the review of last year.

3. Anemia. There has been much discussion of the relation of components of the vitamin B complex and anemia. The original theory that the extrinsic factor of pernicious anemia might be vitamin B_2 (G) was subsequently shown to be erroneous. There has been little evidence to suggest that anemia which may accompany beriberi is due to deficiency of vitamin B_1. Recently Bianco and Jolliffe[161] reported that in 159 of 189 cases of alcohol addiction that condition was "complicated" by one or more of the following disorders: polyneuritis, pellagra, alcoholic stomatitis, encephalopathy and cirrhosis. Macrocytosis of the erythrocytes was noted in 61 per cent of the cases in which there were complications. There was no correlation between macrocytosis and achlorhydria, severity of hepatic damage or presence of an enlarged liver. These investigators concluded, therefore, that the anemia was not a manifestation of inability on the part of the liver to store a hemopoietic principle but of an extrinsic deficiency of some hemopoietic substance required to maintain normocytosis.

4. Gastrointestinal tract. The effects of thiamin deficiency on the gastrointestinal tract are still the subject of debate. As Strauss[147] has recently pointed out, there is considerable evidence to support the contention that changes in the gastrointestinal tract, such as anorexia, glossitis, achlorhydria and diarrhea, and changes in the blood, such as those indicating anemia which occur in a variety of conditions thought to be due to deficiency of vitamin B_1, are at least in part if not entirely manifestations of a deficiency of some portion of the vitamin B complex other than thiamin. It is of much clinical importance that this matter be settled, which it undoubtedly will be when crystalline preparations of the components of the B complex become available.

Cowgill[143] has based many of his studies of the vitamin B_1 requirement of man on the supposition that anorexia is the earliest manifesta-

160. Vitamin B_1 Injections in Acute Neuritis of Lepers, Science News, Science (supp.) **88**:8 (July 1) 1938.

161. Bianco, A., and Jolliffe, N.: The Anemia of Alcohol Addicts, Am. J. M. Sc. **196**:414-420 (Sept.) 1938.

tion of vitamin B_1 deficiency. Schlutz and Knott [162] and others are also of the opinion that the intake of vitamin B_1 is related to the appetite, after observations on the appetite of 54 children carefully observed over a period of thirty-two weeks. After a control period, in which a regular diet containing 260 to 420 international units of vitamin B_1 was given daily, to one group was given stabilized wheat germ and to another crystalline vitamin B_1 as a supplement in amounts of 120 to 200 international units. These supplements produced increases of 17 to 25 per cent in grams of food consumed per child per day. There were no apparent ill effects; growth was not forced, but the supplement did tend to stabilize the appetite. In these studies the stimulation of the appetite seemed to be approximately the same in the group which received wheat germ and the one which received crystalline vitamin B_1.

The effect of vitamin B_1 on the liver is not certain. The occurrence of cirrhosis in chronic alcoholic addicts with or without accompanying signs of vitamin B_1 deficiency has suggested to some clinicians the possibility that cirrhosis might be due to a deficiency of vitamin B. Patek [163] observed 10 patients with cirrhosis to whom he gave the usual treatment for this disease and in addition supplements high in vitamin B content. He concluded that some of the patients responded more satisfactorily to treatment than do patients with cirrhosis to ordinary forms of therapy.

It has long been known that in many cases diarrhea accompanies vitamin B deficiency, and in such cases there has always been the question as to whether the diarrhea led to the development of the deficiency disease or whether the diarrhea was the result of it or both. Dann and Cowgill [164] have recently reported studies of the effect of artificially induced diarrhea on the absorption of vitamin B_1 from the intestine of the dog. Under the conditions of the experiment they observed a decrease in absorption of an appreciable portion of the ingested vitamin, and in some cases the daily intake of the vitamin by mouth had to be increased as much as 70 per cent above the dose which previously had been adequate to prevent the development of anorexia. Of even more practical clinical value may be the report of Cheney,[165] who found that of 13 patients with diarrhea of the type classified as symptomatic diarrhea or that due to irritability of the

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162. Schlutz, F. W., and Knott, E. M.: The Effect of Varied Vitamin B Ingestion upon the Appetite of Children, J. Nutrition **15**:411-427 (May) 1938.

163. Patek, A. J., Jr.: Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, Proc. Soc. Exper. Biol. & Med. **37**:329-330 (Nov.) 1937.

164. Dann, M., and Cowgill, G. R.: The Influence of Diarrhea on the Vitamin B_1 Requirement, Arch. Int. Med. **62**:137-150 (July) 1938.

165. Cheney, G.: Vitamin B_1 and Liver Extract in the Treatment of Non-Specific Chronic Diarrhea and Colitis, to be published.

colon, 10 showed beneficial effects after administration of vitamin B_1. Of interest in this connection is the fact that relatively small doses (in all cases only 1 to 3 mg.) were used, that recurrence of diarrhea generally followed cessation of administration of the vitamin and that in some cases it was necessary to give the vitamin parenterally in order to obtain satisfactory results.

Riboflavin.—During the past year there have been no studies of clinical interest in regard to this substance. Those who may be interested in the nutritional importance of riboflavin are referred to the review of last year and to the articles by Hogan [166] and by Sherman and Lanford [167] in the current series on vitamins in *The Journal of the American Medical Association.* States of deficiency of riboflavin have not been reported in man, and overdoses apparently are not toxic.

Pellagra-Preventive Factor (Nicotinic Acid?).—Since the days of Goldberger there has been much speculation as to the chemical nature of the pellagra-preventive or P-P factor. Within the past fifteen months interest in this subject and consequently in the treatment of pellagra has been tremendously stimulated by the observation that nicotinic acid, isolated originally from rice polishings and yeast by Funk in 1911, has a curative effect in cases of pellagra. In fact, the outstanding development in nutrition during the past year has been in relation to the effect of nicotinic acid in pellagra. The importance of this discovery is difficult to estimate when one considers the number of pellagrins in this country and the rapidly curative effect of such an inexpensive substance as nicotinic acid. Nicotinic acid already has been accepted by the Council on Pharmacy and Chemistry for inclusion in New and Nonofficial Remedies for purposes of standardization and clinical experimentation on its use in pellagra. The experimental dose is 0.5 Gm. in five 0.1 Gm. doses daily.

In a recent study Spies, Bean and Stone [168] reported their observations on the effect of nicotinic acid in a series of 73 patients with pellagra. In this group of patients were included those with endemic pellagra as well as those with the disease secondary to other diseases or to chronic alcoholism. They noted that "within seventy-two hours of administration of large amounts of nicotinic acid, sodium nicotinate, nicotinic acid amide or coramine there was fading of the mucous membrane lesions, blanching of the erythema of the cutaneous lesions when present, a tendency toward the return of normal gastro-intestinal func-

166. Hogan, A. G.: Riboflavin: Physiology and Pathology, J. A. M. A. **110**: 1188-1193 (April 9) 1938.

167. Sherman, H. C., and Lanford, C. S.: Riboflavin: Dietary Sources and Requirements, J. A. M. A. **110**:1278-1280 (April 16) 1938.

168. Spies, T. D.; Bean, W. B., and Stone, R. E.: The Treatment of Subclinical and Classic Pellagra, J. A. M. A. **111**:584-592 (Aug. 13) 1938.

tion [and] remission of mental abnormalities when they were present . . . ." Further observations of note were that there was no special healing effect on the dermatitis in cases in which the continuity of the skin had been broken and in which the lesions were moist and ulcerated or dry and thickened. The peripheral neuritis present in 10 cases was not relieved by nicotinic acid, although the pain and numbness associated with this condition disappeared within forty-eight hours after injection of 50 mg. of vitamin B_1 twice a day.

In another article Spies and his associates [169] have discussed in detail the effect of nicotinic acid on the mental symptoms of pellagra. The most common types of psychoses in pellagra are those associated with loss of memory, disorientation, confusion and confabulation. Excitement, mania, depression and delusions may occur. Other less marked symptoms may be those usually classified as neurasthenic. Apparently nicotinic acid in adequate amounts is a specific therapeutic agent for the acute mental symptoms of pellagra, while psychoses in nonpellagrous patients failed to respond to the administration of this substance. The "prodromal" or "neurotic" symptoms of pellagra usually disappeared after administration of nicotinic acid.

Manson-Bahr and Ransford [170] have emphasized in particular the importance of the use of nicotinic acid in the treatment of stomatitis, which they feel may be pellagra without cutaneous lesions.

Spies and his associates [168] also have recorded the effect of nicotinic acid in 100 adults without pellagra. They noted that in 50 per cent of the cases a dose of 100 mg. on an empty stomach would lead to a cutaneous response consisting of flushing, burning, itching and a sensation of increased local heat in the skin. In occasional subjects there were nausea, vomiting and cramps, but there was no constant deviation in blood pressure or in pulse or respiratory rate.

Is Nicotinic Acid the Only Pellagra-Preventive Factor? The answer to this question is not clearcut as yet, but it probably is to be answered in the negative. Spies and Aring [171] have shown, for example, that the pain and numbness caused by peripheral neuritis of pellagra are not relieved by nicotinic acid, whereas thiamin will promptly relieve them. It has been demonstrated that the healing of well developed cutaneous lesions of pellagra is not apparently stimulated by nicotinic acid. These observations indicate that in the treatment of pellagra a generous diet

169. Spies, T. D.; Aring, C. D.; Gilperin, J., and Bean, W. B.: The Mental Symptoms of Pellagra: Their Relief with Nicotinic Acid, Am. J. M. Sc. **196**: 461-475 (Oct.) 1938.

170. Manson-Bahr, P., and Ransford, O. N.: Stomatitis of Vitamin B_2 Deficiency Treated with Nicotinic Acid, Lancet **2**:426-428 (Aug. 20) 1938.

171. Spies, T. D., and Aring, C. D.: The Effect of Vitamin B_1 on the Peripheral Neuritis of Pellagra, J. A. M. A. **110**:1081-1084 (April 2) 1938.

high in its quantity of vitamins and calories should be as much a part of the treatment as is nicotinic acid.

Further evidence for the multiple nature of the deficiency has been suggested by the experimental work of Helmer and Fouts,[172] who found that rats fed a diet that causes black tongue, which is equivalent to a pellagra-producing diet in man, supplemented only with nicotinic acid grew less than rats fed supplemented diets.

Diagnosis of Pellagra: The diagnosis of pellagra is made on the basis of clinical findings. The specific nature of the response of pellagra to therapy with nicotinic acid may be of some value. Laboratory tests for the disease have not been developed, although Spies and his associates,[173] in confirming the clinical diagnosis, suggested that the presence of increased porphyrinuria may be used as an early objective test.

Therapeutic Doses of Nicotinic Acid and Its Mode of Action: The minimal therapeutic dose of nicotinic acid has not been determined, but it seems to vary from case to case. Ruffin[174] reported that doses of 70 to 100 mg. daily result in prompt recovery and are as effective in the average case of acute pellagra as are doses ten times as large. However, most observers who have studied this problem recommend the use of larger doses.

The usual dose of nicotinic acid employed by Spies and his associates[173] was 50 to 100 mg. five or six times daily, with variations in the daily dose of 50 mg. to 1 Gm. The response of the individual pellagrin may vary considerably, and in some cases it may be necessary to give the substance parenterally.

For "monkey pellagra" Harris[175] suggested that the minimum curative dose of nicotinic acid is approximately 2.5 mg. daily per kilogram. For the dog Elvehjem and his associates[176] found 0.5 to 1.5 mg. per kilogram per day to be a minimum dose.

The amount of nicotinic acid which will prevent relapse of pellagra is also unknown, but Schmidt and Sydenstricker[177] reported that 100

172. Helmer, O. M., and Fouts, P. J.: Multiple Nature of the Deficiency of Blacktongue-Producing Diets as Shown by Studies on Rats, J. Nutrition **16:** 271-277 (Sept.) 1938.

173. Spies, T. D.; Sasaki, Y., and Cross, E.: A Note on the Relationship of Porphyrinuria and Human Pellagra, South. M. J. **31**:483-486 (May) 1938.

174. Ruffin, J. M., in discussion on Spies and others.[168]

175. Harris, L. J.: The Vitamin B_2 Complex: VIII. Further Notes on "Monkey Pellagra" and Its Cure with Nicotinic Acid, Biochem. J. **32**:1479-1481 (Sept.) 1938.

176. Elvehjem, C. A.; Madden, R. J.; Strong, F. M., and Woolley, D. W.: Isolation and Identification of the Anti-Blacktongue Factor, J. Biol. Chem. **123:** 137-149 (March) 1938.

177. Schmidt, H. L., Jr., and Sydenstricker, B. P.: Nicotinic Acid in the Prevention of Pellagra, J. A. M. A. **110**:2065-2066 (June 18) 1938.

mg. orally administered twice weekly was not effective in preventing relapse in patients with chronic pellagra.

The mode of action of nicotinic acid is unknown. The observations of numerous workers suggest that lack of this substance leads to cellular alterations in the alimentary tract, skin and other symptoms.

Vitamin B_6.—Isolation of chemically pure crystals of vitamin B_6 has been reported by Paul György [178] and by Lepkovsky.[179] This component of the vitamin B complex is the rat antidermatitic factor, and its relation to human nutrition is unknown.

VITAMIN C

Chemistry and Physiology.—The chemistry of vitamin C is well established. In a recent review of the subject, King [180] emphasized the important points for those who are interested in them. A fact of importance to pharmacists and physicians is that although vitamin C is easily oxidized, King [180] stated that the dry crystals of the vitamin are stable on exposure to air and daylight at room temperature through a period of several years.

The physiology of vitamin C is of great interest, because of the importance of the vitamin in its most clearly established role of maintaining the physical state of "intercellular material." Because of this function the vitamin is closely related to the metabolism of calcium and to the growth of bones, teeth and other tissues, such as cartilage and white fibrous tissue. While King [181] believes that at present it is impossible to indicate with certainty any specific relation between vitamin C and the enzymes in animal tissues so far as normal physiologic processes are concerned, it is not unlikely that some of the observed effects of vitamin C in activating or inhibiting enzymes will be proved to be physiologically significant. That a close relation may exist between vitamin C and complement has been suggested by the work of Ecker and his associates,[182] who found that the reversible oxidation-reduction behavior of complement, as a single protein substance, is dependent in large part on the ascorbic acid content of the plasma. The normal activity of complement is contingent on its being present in the reduced

178. Isolation of Chemically Pure Crystals of Vitamin B_6, Science News, Science (supp.) **87**:10 (April 29) 1938.

179. Lepkovsky, S.: Crystalline Factor 1, Science **87**:169-170 (Feb. 18) 1938.

180. King, C. G.: The Chemistry of Vitamin C, J. A. M. A. **111**:1462-1464 (Oct. 15) 1938.

181. King, C. G.: The Physiology of Vitamin C, J. A. M. A. **111**:1099-1101 (Sept. 17) 1938.

182. Ecker, E. E.; Pillemer, L.; Wertheimer, D., and Gradis, H.: Ascorbic Acid and Complement Function, J. Immunol. **34**:19-37 (Jan.) 1938.

state, and in this connection vitamin C was found to be the reducing agent of major importance in vivo.

King [181] has stated that the anemia which accompanies depletion of vitamin C is thought to be due primarily to dysfunction of the tissues which form the red blood cells rather than to excessive destruction of cells or specific failure in synthesis of hemoglobin.

Tannhauser and his associates [183] have suggested that ascorbic acid is a powerful activator of serum phosphatase and that the large increase in phosphatase activity of the serum in certain diseases is not due to an actual increase in this enzyme in the circulation but rather to its activation. However, King and Delory [184] were unable to substantiate this finding.

Requirement of vitamin C.—The requirement of man for vitamin C can be stated more accurately than that for any of the other vitamins. Nevertheless the actual requirement can be expressed only in general terms, for it depends on numerous physiologic variables as well as on the method by which the determination is made. The principal methods by which the requirement of vitamin C is determined are the resistance or fragility of blood capillaries, the excretion of ascorbic acid in the urine and the content of ascorbic acid in the blood. After a long discussion of the various phases of this problem Smith [185] has come to the following conclusions:

> Three levels of requirement may be considered in terms of the minimum quantities of ascorbic acid required: (1) to prevent the slightest decrease in capillary resistance or to maintain uniform excretion of the vitamin barely above that on a vitamin C-free diet; (2) to maintain uniform excretion after a depletion period following a preliminary saturation period and (3) to maintain the tissues in a state of saturation as determined by various modifications of the test dose method. These levels of requirement may conveniently be termed the physiologically indispensable, adequate and saturation values respectively.

The range for these three levels may be set between the following limits: for infants, from 8 (newborn) to 50 mg. daily; for children, from 22 to 100 mg. or more, and for adults, from 28 to 100 mg. Values of about 20 mg. daily for infants, 40 mg. for children and from 50 to 60 mg. for adults may be considered as tentative estimates for the middle or barely adequate level of consumption, with but little margin of safety or allowance for individual variation in requirement.

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183. Maddock, S.; Tannhauser, S. J.; Reichel, M., and Gratton, J.: New Conception of Serum Phosphatase; Review of Experimental Work, New England J. Med. **218**:166-169 (Jan. 27) 1938.

184. King, E. J., and Delory, G. E., cited in Serum Phosphatase and Ascorbic Acid, Annotations, Lancet **1**:564-565 (March 5) 1938.

185. Smith, S. L.: Human Requirements of Vitamin C, J. A. M. A. **111**: 1753-1764 (Nov. 5) 1938.

These figures are in essential agreement with those of Hamil and his associates,[186] who concluded from extensive studies of 427 infants that the minimal protective dose of vitamin C for average healthy, artificially fed infants appears to be 10 mg. per day.

There has been some discussion as to whether or not saturation with vitamin C is the truly optimal state of ascorbic acid nutrition. This point is of great practical importance, since few persons, except those to whom the vitamin is given in rather large quantities, are actually saturated with vitamin C. Is there any clinical significance attached to the lack of vitamin C saturation? The answer to this question cannot be satisfactorily given at present, but it seems reasonable to agree with Zilva[187] that the wide margin of "unsaturation" of vitamin C which exists in the case of most persons has no obviously detrimental effect on their health. He feels that to apply to this zone of unsaturation such expressions as "hypovitaminosis C," "latent or potential scurvy" or "vitamin C subnutrition" is not justified by the present state of knowledge.

Vitamin C Content of Foods and Body Fluids.—Chemical methods have rapidly replaced biologic methods of assay of vitamin C, but Bessey[188] has pointed out that while, in general, chemical methods are more rapid and accurate than the latter, they may lack specificity. Even the biologic methods, such as the preventive method, curative method and tooth method, have a degree of uncertainty, because of the unavoidable variation of individual experimental animals and the indefinite nature of the end point.

With regard to determinations by chemical methods, the principal one of which is that with 2, 6-dichlorophenolindophenol, Bessey[188] feels that the errors in determining the vitamin C content of the blood are of about the same order as those for blood sugar tests. Alternative methods based on the reduction of a variety of chemical substances, such as ferrocyanide and phosphotungstic acid, have not been widely adopted, because in some cases these substances react too slowly in acid solution and the color changes often vary with time. Bessey feels that it is important to emphasize that titration of blood and many other substances which have an extremely low vitamin C content has a limited accuracy even when done with greatest care.

Foods which are the richest sources of vitamin C are oranges, lemons, grapefruit (raw or canned), tangerines, tomatoes (raw or canned), fresh strawberries, green peppers and raw cabbage. Eggs and seeds are

186. Hamil, B. M.: Reynolds, L.; Poole, M. W., and Macy, I. G.: Minimal Vitamin C Requirements of Artificially Fed Infants, Am. J. Dis. Child. **56**:561-583 (Sept.) 1938.

187. Zilva, S.: Sufficiency of Vitamin C, Lancet **2**:1509 (Dec. 25) 1937.

188. Bessey, O. A.: Vitamin C: Methods of Assay and Dietary Sources, J. A. M. A. **111**:1290-1298 (Oct. 1) 1938.

devoid of the vitamin, while the vitamin C content of ordinary commercial pasteurized milk is small. In fact, the vitamin C content of milk is oxidized fairly rapidly to an inactive oxidized form. Light, oxygen and riboflavin are factors necessary for this inactivation. In half an hour in sunlight on the doorstep the vitamin C content of a bottle of milk may be reduced 50 per cent, according to Hand, Guthrie and Sharp.[189] In the process of cooking and preparing foods the following factors have a particularly "unfavorable" influence on the vitamin C content: contact with copper utensils, access to air, prolonged heating and alkalinity. While by means of modern commercial methods of canning, with careful control, products can be prepared with a minimum loss of vitamin C, there may be great variation in such products, and one cannot be too sure of the constancy of the vitamin C content of canned products unless it is carefully tested.

The excretion of vitamin C in the urine depends primarily on the relative degree of saturation of the tissues and the immediate intake of vitamin C. The quantity of ascorbic acid in the urine has been used in a variety of ways as a measure of the state of vitamin C of the tissues and the presence or absence of a state of deficiency. However, single specimens of urine may vary so widely in content of vitamin C that the determinations are valueless. The determination of vitamin C in twenty-four specimens of urine has other disadvantages.

The mechanisms by which the kidney excretes vitamin C are those of glomerular filtration and active tubular reabsorption, according to Ralli, Friedman and Rubin,[190] who have stated that the excretion of vitamin C is determined by (1) the plasma level, (2) the rate of glomerular filtration and (3) the maximal rate of tubular reabsorption.

Bessey [188] is of the opinion that rapid direct application of the titration method of determining the content of vitamin C in the blood will for many purposes undoubtedly replace the less practical technic of determining this substance in collected specimens of urine. By means of a single determination of the blood the reserve of vitamin C can be estimated for persons in that wide zone between scurvy and saturation (0.3 and 1.8 mg. per hundred cubic centimeters of blood).

Ascorbic acid is a threshold substance, and Faulkner and Taylor [191] have reported that the critical level of excretion is in the vicinity of 1.4 mg. per hundred cubic centimeters of serum. A blood value of ascorbic

189. Hand, D. B.; Guthrie, E. S., and Sharp, P. E.: Effect of Oxygen, Light and Lactoflavin on Oxidation of Vitamin C in Milk, Science **87**:439-441 (May 13) 1938.

190. Ralli, E. P.; Friedman, G. J., and Rubin, S. H.: The Mechanism of the Excretion of Vitamin C by the Human Kidney, J. Clin. Investigation **17**:765-770 (Nov.) 1938.

191. Faulkner, J. M., and Taylor, F. H. L.: Observations on the Renal Threshold for Ascorbic Acid in Man, J. Clin. Investigation **17**:69-75 (Jan.) 1938.

acid maintained at or above this threshold level corresponds to the so-called saturated state, while values below this correspond to the unsaturated state.

As Wright [192] has stated, "Probably the simplest procedure giving the maximum amount of information is a single determination of cevitamic acid in the blood plasma." The normal level for cevitamic acid in blood plasma for adults lies between 0.7 and 1.3 mg. per hundred cubic centimeters.

It is of interest to note that the blood of the umbilical cord of the human fetus at birth has a content of vitamin C which is two to four times or even more (average, 1.3 mg.) that of maternal plasma taken at the time of delivery. As suggested by Teel and his associates,[193] who made this finding, these figures indicate that there is increased need for vitamin C during pregnancy and that the fetus acts parasitically, "taking what it needs irrespective of the mother." Similar findings have been noted by Manahan and Eastman.[194]

The values for vitamin C in the spinal fluid parallel closely those for vitamin C in the blood. Wortis, Liebmann and Wortis [195] have shown that if the blood content is above 0.7 mg. per hundred cubic centimeters, the value for the spinal fluid is almost invariably normal; however, if the value for the blood is less than 0.4 mg., the spinal fluid value is invariably subnormal.

Diagnosis of Vitamin C Deficiency.—A discussion of the large number of procedures which have been described as having value in the diagnosis of vitamin C deficiency would be beyond the limits of this review. Wright [196] has recently reviewed these various methods and has presented a critical analysis of them.

Of particular interest to clinicians should be an evaluation of various tests of capillary resistance or fragility and of the intradermal test which has recently been described. Tests of this type can be performed simply, while, on the other hand, the determination of vitamin C in the blood

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192. Wright, I. S.: Cevitamic Acid (Ascorbic Acid, Crystalline Vitamin C): A Critical Analysis of Its Use in Clinical Medicine, Ann. Int. Med. **12**:516-528 (Oct.) 1938.

193. Teel, H. M.; Burke, B. S., and Draper, R.: Vitamin C in Human Pregnancy and Lactation, Am. J. Dis. Child. **56**:1004-1010 (Nov.) 1938.

194. Manahan, C. P., and Eastman, N. J.: Cevitamic Acid Content of Fetal Blood, Bull. Johns Hopkins Hosp. **62**:478-481 (May) 1938.

195. Wortis, H.; Liebmann, J., and Wortis, E.: Vitamin C in the Blood, Spinal Fluid and Urine, J. A. M. A. **110**:1896-1899 (June 4) 1938. Liebmann, J.; Wortis, H., and Wortis, E.: Note on Lack of Correlation of Capillary Fragility with Vitamin C Content of Blood, Spinal Fluid and Urine, Am. J. M. Sc. **196**: 388-392 (Sept.) 1938.

196. Wright, I. S.: The Present Status of the Clinical Use of Cevitamic Acid, Am. J. M. Sc. **192**:719-735 (Nov.) 1936; footnote 192.

requires considerable experience and laboratory equipment, and an intravenous test dose of 1,000 mg. of vitamin C entails considerable expense.

Increased fragility of capillaries when due to vitamin C deficiency with occasional exceptions will be restored to normal by the administration of this vitamin to the patient. Wright,[192] who has expressed the opinion that "in spite of all of our chemical procedures to determine saturation, fragility of the minute vessels still remains the first positive clinical measure of the presence of the disease entity—scurvy." This test is not specific, however, and may give positive results in a variety of conditions. Göthlin,[197] who has had much to do with establishing the usefulness of this test, still feels that it retains its clinical value, despite the development of direct chemical methods for the estimation of vitamin C. However, the relation between the number of petechiae which appear under standard conditions and the concentration of ascorbic acid in the blood is not sufficiently exact to permit quantitative predictions.

The method of studying vitamin C saturation and of determining the presence or absence of vitamin C deficiency by means of test doses has been widely used, and there are many reports of various types of tests—the variation is principally in the size of the dose, the method of administration and the period during which the urine is collected for analysis. Wright [192] is of the opinion that a test dose of 1,000 mg. introduced intravenously is the most satisfactory. Normally at least half of this dose is excreted during the following twenty-four hours, and of the 500 mg., 80 per cent appears in the urine within the first five hours. There may be several disadvantages in using such large test doses, for, as pointed out by van Eekelen and Heinemann,[198] intravenous administration of even modest doses or an intake by mouth of an excessively large dose at one time can simulate saturation by causing urinary excretion of a surplus before the depletion of the body has been overcome. Ralli and Friedman [199] are included among those investigators who advocate an intravenous test dose of 100 mg.

Considerable interest was aroused by the suggestion that an intradermal dye test might be of value in the diagnosis of vitamin C deficiency. Portnoy and Wilkinson [200] reported that using the method described by

197. Göthlin, G. F.: When Is Capillary Fragility a Sign of a Subnormal Supply of Vitamin C in Man? Acta pædiat. **20**:71-94, 1937.

198. van Eekelen, M., and Heinemann, M.: Critical Remarks on the Determination of Urinary Excretion of Ascorbic Acid, J. Clin. Investigation **17**:293-299 (May) 1938.

199. Ralli, E. P., and Friedman, G. J.: The Response to the Feeding of Cevitamic Acid in Normal and Deficient Subjects as Measured by a Vitamin C Excretory Test, Ann. Int. Med. **11**:1996-2006 (May) 1938.

200. Portnoy, B., and Wilkinson, J. F.: Vitamin C Deficiency: An Intradermal Test, Brit. M. J. **1**:328-329 (Feb. 12) 1938.

Rotter [201] they obtained results which suggested that the method was a useful, rapid clinical test for vitamin C subnutrition and worthy of further study. The test was based on the fact that since the determination of vitamin C is dependent on the reduction of a blue dye, 2, 6-dichlorophenolindophenol, to its leuko form, the possibility of study in the reduction of the dye by the vitamin C in the skin seemed possible. According to their observations, when decolorization of the dye injected intradermally occurs in less than five minutes, the result indicates saturation of the tissues with vitamin C; while if it occurs in ten minutes or longer, the evidence favors the presence of deficiency of vitamin C. However, Poncher and Stubenrauch [202] were unable to confirm these results and suggested that the data obtained by them indicated that the intradermal dye test in its present form cannot be relied on to give satisfactory clinical information as to the ascorbic acid saturation in the individual case. Wright and MacLenathen [203] also have carefully checked this method and found it unsatisfactory, since the range of error is too great.

Vauthey [204] has reached the conclusion that the "basic ascorburia," a term he applies to the hourly excretion of vitamin C in the urine while the patient is fasting, may be regarded as a physiologic constant and that it may be employed to determine the vitamin C content of the organism or for the detection of latent hypovitaminosis C.

Mělka and Klimo [205] made observations on the vitamin C content of the spinal fluid in 277 cases and found that the detected values were of no diagnostic significance in distinguishing normal persons from those with disorders of the central nervous system.

Relation of Vitamin C to Diseases of the Joints and to Peptic Ulcer.—Vitamin C deficiency has been related to a large variety of diseases, despite the fact, as Finkle [206] has pointed out, that a low body level of vitamin C is the cause of no other disease but scurvy, with the possible exception of lupus erythematosus.

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201. Rotter, H.: Determination of Vitamin C in the Living Organism, Nature, London **139**:717 (April 24) 1937; Bestimmung des Vitamins C im lebenden Organismus, Wien. klin. Wchnschr. **51**:205-206 (Feb. 18) 1938.

202. Poncher, H. G., and Stubenrauch, C. H., Jr.: Intradermal Dye Test for Vitamin C Deficiency, J. A. M. A. **111**:302-304 (July 23) 1938.

203. Wright, I. S., and MacLenathen, E., cited by Wright.[192]

204. Vauthey, M.: Etudes sur le métabolisme de la vitamine C: valeurs de l'ascorburie de base au cours du métabolisme normal, Arch. d. mal. d. l'app. digestif **28**:230-235 (March) 1938; abstracted, J. A. M. A. **110**:1963 (June 4) 1938.

205. Mělka, J., and Klimo, Z.: Ascorbinsäuregehalt in der Cerebrospinalflüssigkeit des Menschen, Klin. Wchnschr. **17**:302-303 (Feb. 26) 1938.

206. Finkle, P.: Vitamin C Saturation Levels in Body in Normal Subjects and in Various Pathological Conditions, J. Clin. Investigation **16**:587-593 (July) 1937.

The observation of Rinehart and his associates [207] that the vitamin C level of the blood plasma during fasting is almost uniformly and severely lowered in rheumatoid arthritis and rheumatic fever was interpreted by them as affording significant support for the thesis that chronic deficiency of vitamin C is an important factor in the causation of these diseases. However, a majority of other investigators in discussing this work are not in agreement with this opinion. Keith and Hichmans,[208] who have made a more recent contribution to this subject, found no direct evidence to support the theory that rheumatic fever is a manifestation of vitamin C deficiency associated with an infection.

The interesting problem of the possible relation of peptic ulcer to deficiency of vitamin C and more particularly of hemorrhage from an ulcer to deficiency of vitamin C remains unsolved. Portnoy and Wilkinson [209] have reported careful studies of a group of 107 subjects (51 controls, 25 patients with ulcer and 31 with hematemesis) on whom six methods for determining vitamin C nutrition were studied, based on urinary excretion, the saturation test, the initial plasma values, tolerance for ascorbic acid given orally, tolerance for ascorbic acid given intravenously and the intracutaneous test. According to all these tests, patients with peptic ulcer, especially those with bleeding, presented evidence suggestive of vitamin C deficiency. Almost all other workers, for instance, Rivers and Carlson,[210] Ingalls and Warren,[211] Bourne [212] and Chamberlin and Perkins,[213] agree that patients with peptic ulcer, even those receiving an approved diet for ulcer, have lower levels of ascorbic acid in the blood and urine than have normal persons. However, as

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207. Rinehart, J. F.; Greenberg, L. D.; Baker, F.; Mettier, S. R.; Bruckman, F., and Choy, F.: Metabolism of Vitamin C in Rheumatoid Arthritis, Arch. Int. Med. **61**:537-551 (April) 1938. Rinehart, J. F.; Greenberg, L. D.; Olney, M., and Choy, F.: Metabolism of Vitamin C in Rheumatic Fever, ibid. **61**:552-561 (April) 1938.

208. Keith, J. D., and Hickmans, E. M.: Vitamin C Excretion in Children with Particular Reference to Rheumatic Fever, Arch. Dis. Childhood **13**:125-136 (June) 1938.

209. Portnoy, B., and Wilkinson, J. F.: Vitamin C Deficiency in Peptic Ulceration and Hematemesis, Brit. M. J. **1**:554-560 (March 12) 1938.

210. Rivers, A. B., and Carlson, L. A.: Vitamin C as a Supplement in the Therapy of Peptic Ulcer, Proc. Staff Meet., Mayo Clin. **12**:383-384 (June 16) 1937.

211. Ingalls, T. H., and Warren, H. H.: Asymptomatic Scurvy: Its Relation to Wound Healing and Its Incidence in Patients with Peptic Ulcer, New England J. Med. **217**:443-446 (Sept. 9) 1937.

212. Bourne, G.: Vitamin C Deficiency in Peptic Ulceration Estimated by the Capillary Resistance Test, Brit. M. J. **1**:560-562 (March 12) 1938.

213. Chamberlin, D. T., and Perkins, J. J.: The Level of Ascorbic Acid in the Blood and Urine of Patients with Peptic Ulcer, Am. J. Digest. Dis. **5**:493-497 (Oct.) 1938.

Jones and his collaborators [214] have pointed out in their review of gastroenterology, it is highly probable that these findings represent the results of a deficiency secondary to the original ulcer condition, rather than that there is a causative relation to the formation of ulcer. The latter authors have stated that it is probable that the intelligent administration of vitamin C to patients with ulcer who show a lack of vitamin C is a rational therapeutic procedure. Chamberlin and Perkins [213] were unable to find any clinical evidence that ascorbic acid in doses large enough to maintain the excretion at a normal level was of any value in the treatment of patients with peptic ulcer with or without hemorrhage.

Therapy with Vitamin C.—Treatment with vitamin C is generally simple. Foods rich in the vitamin form the basis for any therapeutic approach in most cases in which deficiency of vitamin C is suspected or found. Curative doses of crystalline preparations of the vitamin vary from 30 to 1,000 mg. daily. Occasionally patients will be unable to absorb appreciable quantities of the vitamin from the gastrointestinal tract, and it may be necessary to administer the vitamin to them either intramuscularly (up to 100 mg.) or intravenously. Overdosage is not harmful, as the toxicity of ascorbic acid is low. As Wright [192] has pointed out, most patients with scurvy can be cured with ascorbic acid. A few seem resistant to this substance, whereas they can be cured by the administration of large doses of lemon juice or the juice of other citric fruits.

Vitamin C therapy has been recommended also in the treatment of heart failure (Evans [215]), insomnia (Maurer and his associates [216]), diabetes (Pfleger and Scholl [217]), asthma (Hunt [218] and Hagiesco and his associates [219]), urticaria (Rosenberg [220]) and a variety of other conditions, but the value of ascorbic acid in these conditions and conditions other than scurvy remains to be demonstrated.

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214. Jones, C. M.; Urmy, T. V.; Benedict, E. B.; Clifford, M. H., and White, B. V.: Gastroenterology: A Review of the Literature from January 1937 to June 1938, Arch. Int. Med. **62**:652-718 (Oct.) 1938.

215. Evans, W.: Vitamin C in Heart Failure, Lancet **1**:308-309 (Feb. 5) 1938.

216. Maurer, S.; Wiles, H. O.; Schoeffel, E. W., and Fisher, M. L.: The Effect of L-Cevitamic Acid on Insomnia, Illinois M. J. **74**:84-85 (July) 1938.

217. Pfleger, R., and Scholl, F.: Diabetes und Vitamin C, Wien. Arch. f. inn. Med. **31**:219-230, 1937; abstracted, J. A. M. A. **110**:246 (Jan. 15) 1938.

218. Hunt, H. B.: Ascorbic Acid in Bronchial Asthma, Brit. M. J. **1**:726-727 (April 22) 1938.

219. Hagiesco, D.; Bazavan, G.; Criscota, M., and Cioranesco, M.: Essais de traitement de l'asthme pulmonaire por l'acide ascorbique lévogyre (vitamine C), Presse méd. **46**:1435-1438 (Sept. 28) 1938; abstracted, J. A. M. A. **111**:1885 (Nov. 12) 1938.

220. Rosenberg, W. A.: Vitamin C Deficiency as Cause of Urticaria, Arch. Dermat. & Syph. **37**:1010-1014 (June) 1938.

VITAMIN D

Chemistry and Physiology.—The antirachitic effect of vitamin D is possessed by at least ten different sterols, according to Bills.[221] The two most important of these sterols in medicine are activated ergosterol and activated 7-dehydrocholesterol. The vitamin D of viosterol, irradiated yeast and yeast milk is identical and consists of activated ergosterol and calciferol. On the other hand, 7-dehydrocholesterol appears to be the principal activatable sterol or provitamin in cholesterol, the chief sterol of animal fats. It therefore comprises the vitamin D present in irradiated milk, it is produced in the skin on exposure to ultraviolet radiation and it is probably the chief although not the only form of vitamin D in fish oils.

Heymann [222] has produced evidence from experiments on rats that the liver plays an important role in the antirachitic function of vitamin D. By producing impairment of hepatic function in rats by means of carbon tetrachloride or by ligation of the common bile duct, he found that from two to three and from ten to twelve times, respectively, as much vitamin D in the form of viosterol in oil given intramuscularly was necessary to cure experimental rickets as to cure rickets in control animals without hepatic damage. In another study Heymann [223] observed that vitamin D is excreted through the intestinal wall, particularly in the upper third of the small intestine, when it is given parenterally to dogs with obstruction of the common bile duct.

The exact function of vitamin D in relation to calcium and phosphorus metabolism and to the parathyroid glands is still not clear. In a review of the physiology of vitamin D, Shohl [224] pointed out that the main action of the vitamin is to increase the absorption of calcium and phosphorus or to diminish their intestinal excretion. In an effort further to elucidate this complicated and confusing problem, Albright and Sulkowitch [225] have recently reported careful metabolic studies on 4 patients. They have pointed out that of the two hypothesized fundamental actions of vitamin D to decrease the fecal excretion of calcium and to increase the urinary excretion of phosphorus, it should be noted that the former would tend to heal rickets and the latter would tend toward demineraliza-

221. Bills, C. E.: The Chemistry of Vitamin D, J. A. M. A. **110**:2150-2155 (June 25) 1938.

222. Heymann, W.: Metabolism and Mode of Action of Vitamin D: III. Importance of the Liver for Its Antirachitic Efficacy, Am. J. Dis. Child. **55**:913-923 (May) 1938.

223. Heymann, W.: Metabolism and Mode of Action of Vitamin D: V. Intestinal Excretion of Vitamin D, J. Biol. Chem. **122**:257-262 (Dec.) 1937.

224. Shohl, A. T.: Physiology and Pathology of Vitamin D, J. A. M. A. **111**:614-619 (Aug. 13) 1938.

225. Albright, F., and Sulkowitch, H. W.: The Effect of Vitamin D on Calcium and Phosphorus Metabolism: Studies on Four Patients, J. Clin. Investigation **17**:305-315 (May) 1938.

tion of bone. On the basis of the values for serum calcium and phosphorus, they hypothecated three types of vitamin D deficiency:

(*a*) Normal calcium and a low phosphorus—where parathyroid hyperplasia has not occurred; (*b*) normal calcium and a low phosphorus—where parathyroid hyperplasia has compensated for low calcium and (*c*) low calcium, low phosphorus—where parathyroid hyperplasia has occurred but is unable to compensate for low calcium.

Requirement of Vitamin D.—The requirement of vitamin D may be defined, according to Jeans and Stearns,[226] as the amount which, with an ample intake of calcium and phosphorus and a diet otherwise adequate, will insure sufficient retention of calcium and phosphorus to permit (*a*) normal growth and mineralization of the skeleton and teeth of infants and children, (*b*) maintenance of bony and dental structures during adult life and (*c*) a sufficient supply for mother and infant during pregnancy and lactation.

The Council on Foods of the American Medical Association[227] recently investigated the matter of the vitamin D requirement of premature infants and found that there is evidence that prevention of rickets in premature infants may be accomplished by administration of about 70 U. S. P. units of vitamin D per kilogram of body weight. However, for adequate retention of calcium and phosphorus and for growth it is concluded that from 600 to 800 U. S. P. units of vitamin D fed in dispersed form will satisfy the requirements. This is approximately twice the requirement for prevention of rickets and for growth of the majority of full term infants. The Council noted that the claim be recognized that infants receiving customary quantities of milk containing 400 U. S. P. units of vitamin D per quart exhibit good growth.

For adolescents a need for vitamin D exists, but according to Jeans and Stearns,[226] insufficient data are available to permit an estimate of the quantity required. An estimate of 300 to 400 U. S. P. units daily is suggested. For adults the optimal amount of vitamin D, if a need exists, remains to be determined. During pregnancy and lactation 800 U. S. P. units or more is suggested.

Treatment with Vitamin D.—The prevention and treatment of rickets have become greatly simplified since vitamin D has been available in the form of cod liver oil concentrate and vitamin D milk. Almost all pediatricians and physicians have developed or accepted methods of therapy which have proved to be highly effective. An excellent summary of this subject has been prepared by Park.[228] An interesting contribution

226. Jeans, P. C., and Stearns, G.: The Human Requirements of Vitamin D, J. A. M. A. **111**:703-711 (Aug. 20) 1938.

227. Annual Meeting of the Council on Foods, report of the Council on Foods, J. A. M. A. **111**:156-157 (July 9) 1938.

228. Park, E. A.: The Use of Vitamin D Preparations in the Prevention and Treatment of Disease, J. A. M. A. **111**:1179-1187 (Sept. 24) 1938.

in this connection and one which at the same time should provoke physiologic discussion of the function of vitamin D is that of Braulke [229] concerning *Vitaminstoss* therapy. In 1935 Harnapp discovered accidentally that a single large dose of vitamin D produced prompt and rather lasting effects in healing rickets. Braulke advanced the technic of this method of therapy, gave it its name and reported the results of its use in 50 cases with no ill effects. He administered in a single dose about 15 mg. of calciferol (600,000 U. S. P. units of vitamin D) as compared to an ordinary dose of 3,000 U. S. P. units. Within a few days healing was noted in roentgenograms, and the process proceeded to completion without further treatment. He feels that there are indications for using this method of therapy: (1) in manifest and latent tetany, (2) in

TABLE 3.—*Daily Requirements of Vitamins*

	Infant and Child	Adult	Pregnancy and Lactation	Suggested Optimal Amount for Adults	Therapeutic Doses
Vitamin A, U.S.P. units	6,000-8,000*	2,000-4,000†	5,000+*	8,000-10,000	10,000-60,000
Vitamin B_1					
International units	200-250‡	200-500[138]	600-700[143]	500	2,500-15,000
Milligrams	1.0-1.5‡	1-2[138]	2.5-3[143]	2	10-60
Nicotinic acid, mg	?	?	?	?	200-500[168]
Riboflavin, mg	?	?	?	2-3[166] (suggested)	?
Vitamin B_6	?	?	?	?	?
Vitamin C, mg	40-100[185]	50-100[185]	60-100[185]	80-100[185]	25-3,000
Vitamin D, U.S.P. units	400-600§	?	800-1,000[226]	?	400-1,000,000

* Report on the Physiological Bases of Nutrition, by the Technical Commission appointed by the Health Committee, League of Nations, Publication C. H. 1197, Geneva, Switzerland, World Peace Foundation, 1935.

† Report by the Technical Commission on Nutrition on the Work of Its Third Session, Bull. Health Organ., League of Nations **7**:460 (June) 1938.

‡ Report by the Technical Commission on Nutrition on the Work of Its Third Session, Bull. Health Organ, League of Nations **7**:461 (June) 1938; cited by Baker, A. Z.: Human Requirements for Vitamin B_1, J. A. M. A. **111**:1866 (Nov. 12)1938.

§ For the premature infant 600 to 800 U.S.P. units [227] and for the growing child 300 to 400 U.S.P. units [226] daily.

moderate and severe rickets with acute or chronic infection, (3) in rachitis gravis and (4) in cases in which the likelihood of adequate treatment at home is unsatisfactory.

A variety of dissimilar clinical conditions have been treated with massive doses of vitamin D. There has been little change in the status of this type of therapy in chronic arthritis during the past year. Abrams and Bauer [230] have summarized their experiences in this regard by

229. Braulke, H.: Die Indikationen der Rachitisbehandlung mit einmaliger Dosis von Vitamin D_2 (Vitaminstoss), Ztschr. f. Kinderh. **59**:18-31, 1937; abstracted, Am. J. Dis. Child. **56**:643-644 (Sept.) 1938.

230. Abrams, W. R., and Bauer, W.: The Treatment of Rheumatoid Arthritis with Large Doses of Vitamin D, J. A. M. A. **111**:1633-1639 (Oct. 29) 1938.

stating that the results they have obtained indicate that the administration of massive doses of vitamin D in rheumatoid arthritis is of little or no value in alleviating the cause of the disease and does not justify the expense and dangers involved.

Concerning cases of psoriasis, Ceder and Zon [231] have presented some interesting observations. In a series of 15 patients with widespread chronic psoriatic lesions to whom was given from 300,000 to 400,000 U. S. P. units of vitamin D daily, these observers have reported that 11 showed complete involution of the lesions within six to twelve weeks. After cessation of the treatment there was recurrence of the lesions in some of the cases, although the degree of severity of the lesions was much less than was observed before. Care must be used to avoid producing evidence of hypervitaminosis D with this form of treatment.

Maynard [232] has reported encouraging results in the treatment of acne with doses of viosterol varying from 20 to 40 drops daily. Knapp [233] is of the opinion that keratoconus, a rare disease of the eye, can be reproduced in rats and dogs with diets deficient in vitamin D and calcium. He gave vitamin D and calcium to 11 patients with the disease and was able to produce gratifying results in all instances. However, Laval [234] was unable to confirm previously made observations that vitamin D and calcium help patients who have myopia by reducing the amount of myopia, by keeping it stationary or by preventing as rapid an increase in the process as is usually found in patients who have not used this form of therapy.

The Treatment of Parathyroid Tetany with Dihydrotachysterol.—One of the most troublesome, even though infrequent, complications of surgical treatment of diseases of the thyroid gland is postoperative tetany. A majority of the patients have responded satisfactorily to administration of calcium, vitamin D and parathyroid extract. However, in all cases this type of therapy has not been successful. In the past year MacBryde [235] has reported an even more successful therapeutic agent, namely, dihydrotachysterol, which is a derivative of viosterol. By employing it orally in an oily solvent (5 mg. per cubic centimeter), MacBryde reported that for the first time he had been able to maintain

231. Ceder, E. T., and Zon, L.: Treatment of Psoriasis with Massive Doses of Crystalline Vitamin D and Irradiated Ergosterol: Preliminary Report, Pub. Health Rep. **52**:1580-1584 (Nov. 5) 1937.

232. Maynard, M. T. R.: Vitamin D in Acne: Comparison with X-Ray Treatment, California & West. Med. **49**:127-132 (Aug.) 1938.

233. Knapp, A. A.: Vitamin D Complex in Keratoconus, J. A. M. A. **110**: 1993-1994 (June 11) 1938.

234. Laval, J.: Vitamin D and Myopia, Arch. Ophth. **19**:47-53 (Jan.) 1938.

235. MacBryde, C. M.: The Treatment of Parathyroid Tetany with Dihydrotachysterol, J. A. M. A. **111**:304-307 (July 23) 1938.

patients with chronic tetany free from symptoms and to maintain the calcium content of the blood at normal levels. Dihydrotachysterol alone will raise the serum calcium value to normal, but daily doses of 1 to 2 cc. are necessary if no calcium is added to the usual diet. By supplementing the diet with calcium lactate or gluconate in doses of 4 to 10 Gm. a day, approximately normal levels of serum calcium can be maintained with doses of from 0.3 to 1 cc. of dihydrotachysterol daily. After the administration of this substance the first increase in the calcium value occurs in about forty-eight hours, and in seven to fourteen days normal levels are reached. Pickhardt and Bernhard [236] have also reported excellent results with dihydrotachysterol in the treatment of 5 patients with tetany following an operation on the thyroid. The mechanism of action of the sterol is not clear as yet, but so far as is known the results of therapy persist only so long as the treatment is continued. Excessive doses produce hypercalcemia and severe toxic effects.

Albright and his associates [237] have studied the action of dihydrotachysterol and vitamin D on the calcium and phosphorus metabolism of 3 patients with hypoparathyroidism. They are of the opinion that the two substances have the same fundamental action, namely, to increase the absorption of calcium from the intestinal tract and to increase the excretion of phosphorus in the urine. The ratio of the latter action to the former, however, was apparently greater with dihydrotachysterol than with vitamin D, which may explain why dihydrotachysterol is not antirachitic. The action of parathyroid extract resembled that of dihydrotachysterol as regards its property of causing a markedly increased urinary excretion of phosphorus but differed in that it probably had no primary action on the absorption of calcium from the intestinal tract.

DENTAL CARIES

The occurrence of dental caries is so widespread and the disorder leads to so much discomfort and ill health that it is surprising that more attention is not paid to the problem, particularly by physicians. There are in essence two schools of thought in regard to the fundamental causes of dental caries—one which believes that the disease is the result of inadequate nutrition of the individual or of his teeth and the other which believes that the important etiologic factor is the environment of the teeth in the mouth, particularly in regard to the occurrence of con-

236. Pickhardt, O. C., and Bernhard, A.: Treatment of Postoperative Tetany with Dihydrotachysterol, Ann. Surg. **108**:362-373 (Sept.) 1938.

237. Albright, F.; Bloomberg, E.; Drake, T., and Sulkowitch, H. W.: A Comparison of the Effects of A.T. 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism, J. Clin. Investigation **17**:317-329 (May) 1938.

ditions which make it possible or impossible for organisms to infest the mouth and to produce acid. Koehne,[238] who has been much interested in this problem, recently summarized the known facts in regard to it so well that her conclusions deserve repetition in a place where physicians may see them:

1. It has been impossible to produce caries in most experimental animals. Its recent production in rats was brought about by dietary conditions affecting the environment of the molars.

2. Not all teeth in the mouth are equally susceptible.

3. Cavities begin in highly protected areas on the outside of the tooth.

4. Not all poorly enameled teeth are susceptible to caries.

5. Not all well-enameled teeth are free from caries.

6. Some persons are free from caries even though their diets have long been very inadequate nutritionally.

7. Other persons are susceptible to caries even though they have long been accustomed to well-balanced diets.

8. Caries can be produced in persons on well-balanced diets by additions to the diet of such a nature that their only known measurable effect is the increase in concentration of aciduric organisms in the saliva.

The nutritional adequacy or inadequacy of the diet may be a factor in determining the rate of progress of caries, but is probably not its primary etiologic agent. Saliva may contain a factor or factors that minimize the effect of acid formed on the tooth surface. The nature of this factor is not yet known.

The nature of true immunity is not yet known. It is doubtless an inherited characteristic. There is evidence that it inhibits the growth of certain aciduric micro-organisms in the body.

There are many legitimate reasons for recommending that the diet of children and adults be nutritionally adequate. If, at the same time, the use of concentrated sweets is reduced to an absolute minimum, there is the greatest likelihood that the incidence of caries in the civilized population of the world will be reduced to a minimum.

VITAMIN E

References to vitamin E are to be found in the literature principally in journals dealing with biochemistry and with obstetrics and gynecology. Internists have been unable to find clinical usefulness for it.

Several substances, including alpha and beta tocopherol, have vitamin E activity. Evans and the Emersons[239] reported during the past year that the feeding of durohydroquinone and of various of its esters and certain cyclic ethers indicates that vitamin E activity is displayed by some of these substances when fed at high levels. Synthetic alpha-

238. Koehne, M.: Relation of Diet to Oral Health, J. Am. Dent. A. **25**: 1767-1780 (Nov.) 1938.

239. Evans, H. M.; Emerson, G. A., and Emerson, O. H.: The Chemistry of Vitamin E: II. Biological Assays of Various Synthetic Compounds, Science **88**:38-39 (July 8) 1938.

tocopherol was as effective as the same substance secured from natural sources.

Shute [240] and more recently Currie [241] have reported the favorable effects of vitamin E in wheat germ oil on patients with habitual abortion, and the former author has suggested that vitamin E and estrogen or a substance much like it exist in a sort of equilibrium in pregnancy. If there is too much of the estrogenic substance, the pregnancy is terminated.

The presence of a neurotropic factor in wheat germ oil and the effect of chronic vitamin E deficiency on the nervous system and the skeletal musculature of adult rats are the subjects of a monograph by Einarson and Ringsted.[242]

VITAMIN K

There has been much interest during the past year in a possible relation between deficiency of vitamin K and the hemorrhagic tendency in jaundice. This substance or group of substances, which originally was associated only with a hemorrhagic disease in chicks, has risen to clinical interest because of observations of a deficiency of prothrombin in the plasma of chicks with vitamin K deficiency and of dogs and of men with various diseases of the biliary tract and liver.

As Snell, Butt and Osterberg [243] have pointed out, a deficiency of prothrombin occurs in chicks fed on diets lacking in certain fat-soluble substances, in experimental animals with external or renal biliary fistulas, in dogs whose livers have been injured by chloroform and in cattle fed on toxic sweet clover hay. They believe two factors, the presence of bile in the bowel and the presence of a hypothetic fat-soluble vitamin, are of importance in maintaining a normal concentration of prothrombin in the blood. A third and equally important factor is that which has to do with the fabrication, storage or activation of prothrombin, which apparently occurs in the liver. If these hypotheses are correct, the most likely causes of prothrombin deficiency and therefore of the hemorrhagic tendency in jaundice are failure of absorption of vitamin K in adequate amounts and interference with the metabolism of prothrom-

240. Shute, E.: Early Diagnosis of Abruptio Placentae and Its Treatment with Wheat Germ Oil, Am. J. Obst. & Gynec. **33**:429-436 (March) 1937.

241. Currie, D.: Vitamin E in Treatment of Habitual Abortion, Brit. M. J. **2**:1218-1220 (Dec. 18) 1938.

242. Einarson, L., and Ringsted, A.: Effect of Chronic Vitamin E Deficiency on the Nervous System and Skeletal Musculature in Adult Rats: A Neurotropic Factor in Wheat Germ Oil, translated by H. Andersen, New York, Oxford University Press, 1938.

243. Snell, A. M.; Butt, H. R., and Osterberg, A. E.: The Treatment of the Hemorrhagic Tendency in Jaundice, with Special Reference to Vitamin K, Am. J. Digest. Dis. **5**:590-596 (Nov.) 1938.

bin as a result of hepatic damage. Smith and his associates [244] have recently shown that in the absence of bile in the intestines, fat-soluble vitamin K is poorly absorbed.

Further evidence of the importance of the liver in this problem is indicated by a recent report of Lichtman and Chambers,[245] who were able to obtain evidence indicating that the liver contains a sterol which is active in reducing the clotting time of the blood of normal and jaundiced dogs. The extract was similar in action to vitamin K but differed from it in several clinical properties.

Snell and his associates [243] have not observed an abnormal tendency to bleed in any jaundiced patient with a normal prothrombin value. To what degree must the prothrombin level fall before the hemorrhagic tendency appears? Warner, Brinkhous and Smith [246] have suggested that for the dog this critical condition occurs when the prothrombin reaches a level of 20 to 30 per cent of the normal content. As long as the content of prothrombin remains above this point, no marked prolongation of coagulation time occurs. This observation may explain why patients with jaundice at times bleed abruptly and unexpectedly, for a small loss of prothrombin by a patient whose plasma content is near the "critical" level might presumably bring the level below the point required for the formation of a clot.

The effects of administering vitamin K to more than 30 patients have been reported by Butt and his associates.[247] They used concentrates prepared from putrefied fish meal or extracted from alfalfa together with bile salts or human bile. Apparently when administered to jaundiced patients by mouth vitamin K must be accompanied by bile or bile salts to be absorbed. Administration of these two substances to patients who have jaundice has been followed by an elevation in the quantitative level of prothrombin in the circulating blood and by a reduction in the elevated prothrombin clotting time, and in 13 cases actual bleeding has been controlled.

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244. Smith, H. P.; Warner, E. D.; Brinkhous, K. M., and Seegers, W. H.: Bleeding Tendency and Prothrombin Deficiency in Biliary Fistula Dogs: Effect of Feeding Bile and Vitamin K, J. Exper. Med. **67**:911-920 (June) 1938.

245. Lichtman, A. L., and Chambers, W. H.: Reduced Blood Coagulation Time by Injection of Sterol Extract of Liver, Science **88**:358-359 (Oct. 14) 1938.

246. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**:667-675 (Feb.) 1936.

247. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: Further Observations on the Use of Vitamin D in the Prevention and Control of the Hemorrhagic Diathesis in Cases of Jaundice, Proc. Staff Meet., Mayo Clin. **13**:753-764 (Nov. 30) 1938.

The desirability of using a preparation of vitamin K which may be given parenterally is obvious, particularly for use in those cases in which because of injury to the liver large amounts of the vitamin are required to obtain the desired effect. Emulsions of the vitamin have been used intramuscularly by Dam and Glavind,[248] with return to normal of the clotting power of the blood of 5 patients who had obstructive jaundice and deficiency of blood coagulation. However, Butt, Snell and Osterberg[247] have reported that the concentrates which they used intramuscularly did not effectively alter extremely high prothrombin levels, although they are of the opinion that this method of administration may be of some prophylactic use after operation.

Almquist[249] and Doisy and his collaborators[250] have reported obtaining vitamin K in crystalline form. The latter observers[251] have also reported that minute amounts of vitamin K permit complete recovery within a few days from the anemia which accompanies vitamin K deficiency.

OTHER SO-CALLED VITAMINS AND ESSENTIAL SUBSTANCES

Vitamin F.—Certain essential unsaturated fatty acids, such as linoleic acid, have been called vitamin F by some investigators. Burr and his associates[252] made further studies of these substances and found that the human subject requires preformed unsaturated fatty acid in the diet and that arachidonic acid is effective as a curative agent in relieving the condition which is caused by deficiency of essential unsaturated fatty acids. It is suggested by the observations of Turpeinen[253] that at least two double bonds appear necessary for fatty acids to be effective in curing "fat deficiency" disease; these double bonds must occupy the position 9:10 and 12:13 to possess the features which are responsible for the curative properties of an eighteen carbon atom fatty acid.

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248. Dam, H., and Glavind, J.: Clotting Power of Human and Mammalian Blood in Relation to Vitamin K, Acta med. Scandinav. **96**:108-128, 1938.

249. Almquist, H. J.: Further Studies on the Anti-Hemorrhagic Vitamin. J. Biol. Chem. **120**:635-640 (Sept.) 1937.

250. Thayer, S. A.; MacCorquodale, D. W.; Binkley, S. B., and Doisy, E. A.: The Isolation of a Crystalline Compound with Vitamin K Activity, Science **88**: 243 (Sept. 9) 1938.

251. Thayer, S. A.; McKee, R. W.; MacCorquodale, D. W., and Doisy, E. A.: Recovery from the Anemia Caused by a Diet Deficient in Vitamin K, Proc. Soc. Exper. Biol. & Med. **39**:417-480 (Nov.) 1938.

252. Brown, W. R.; Hansen, A. E.; Burr, G. O., and McQuarrie, I.: Effects of Prolonged Use of Extremely Low Fat Diet on Adult Human Subject, J. Nutrition (supp.) **15**:13 (June) 1938. Burr, G. O.; Kass, J. P.; Brown, J. B., and Frankel, J.: On the Fatty Acids Essential in Nutrition, ibid. **15**:15 (June) 1938.

253. Turpeinen, O.: Further Studies on the Unsaturated Fatty Acids Essential in Nutrition, J. Nutrition **15**:351-366 (April) 1938.

Vitamin P.—There is a divergence of opinion in regard to the existence of vitamin P, also known as citrin or the vitamin of permeability (described by Szent-Györgyi [254]). Lajos,[255] who believes the substance is a mixture of glucosides that belong to the group of the flavones, has reported favorable results in arresting the hematuria of hemorrhagic nephritis with citrin. Jersild [256] has reported the favorable response of a young woman with Schönlein-Henoch purpura to the use of citrin.

Zilva [257] and others do not believe that the vitamin exists.

Vitamin M.—Day, Langston and Darby [258] have described a deficiency syndrome observed in monkeys and characterized by anemia, leukopenia and loss of weight, with ulceration of the gums and diarrhea. They have reported that this syndrome could be prevented by administration of liver extract or yeast but not by the use of moderate doses of riboflavin, nicotinic acid or thiamin. They have termed the unknown etiologic factor vitamin M.

Anti-Gizzard-Erosion Factor.—Additional evidence regarding this substance has been presented by Cheney [259] and by Bird and Oleson.[260] The latter authors found that chondroitin exerted a marked protective action against lesions of the gizzard when fed to chicks at a level of 3 to 5 per cent of the ration. Preparations of greater purity appeared to be more potent than crude preparations.

Since the report by Dam [261] of the occurrence of erosions in the gizzard of chicks with hemorrhagic disease, there has been speculation of the possible relation of the anti-gizzard-erosion factor to vitamin K. Further support for the idea that they are separate substances is given in the work of Almquist.[262]

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254. Bentsáth, A.; Rusznyák, S., and Szent-Györgyi, A.: Vitamin P, Nature, London **139**:326-327 (Feb. 20) 1937.

255. Lajos, S.: Klinische Erfahrungen mit "Citrin" (Vitamin "P"), Klin. Wchnschr. **16**:1615-1617 (Nov. 13) 1937; abstratced, J. A. M. A. **110**:245 (Jan. 15) 1938.

256. Jersild, T.: Therapeutic Effect of Vitamin P in Schönlein-Henoch Purpura, Lancet **1**:1145-1447 (June 25) 1938.

257. Zilva, S. S.: Vitamin P, Biochem. J. **31**:915-919 (June) 1937.

258. Day, P. L.; Langston, W. C., and Darby, W. J.: Failure of Nicotinic Acid to Prevent Nutritional Cytopenia in the Monkey, Proc. Soc. Exper. Biol. & Med. **38**:860-863 (June) 1938.

259. Cheney, G.: Gastric Acidity in Chicks with Experimental Gastric Ulcer, Am. J. Digest. Dis. **5**:104-107 (April) 1938.

260. Bird, H. R., and Oleson, J. J.: Effectiveness of Chrondroitin as the Anti-Gizzard Erosion Factor Required by Chicks, J. Biol. Chem. **123**:xi-xii (May) 1938.

261. Dam, H.: Cholesterinstoffwechsel in Hühnereiern und Hühnchen, Biochem. Ztschr. **215**:475-492, 1929.

262. Almquist, H. J.: Influence of Bile Acids on Erosions of the Chick Gizzard Lining, Science **87**:538 (June 10) 1938.

THE INCIDENCE AND DIAGNOSIS OF VITAMIN DEFICIENCY STATES

Classic examples of well established deficiency diseases, with the exception of rickets and pellagra, are uncommon in this country. However, it is becoming generally agreed that mild states of suboptimal nutrition or borderline states of partial deficiency are common (Minot [263]). It is in conditions of this type that clinical recognition is difficult, because the deficiency is due principally to biochemical or physiologic rather than to pronounced pathologic alterations.

General and sweeping statements regarding the widespread presence or absence of deficiency diseases are made not infrequently but are difficult to prove or disprove. A Committee on Nutritional Problems of the American Public Health Association has recently issued a report on this subject entitled "Extent of Vitamin Deficiency in the United States." [264] The report consists chiefly of a discussion of various measures which have been suggested as diagnostic procedures for determining vitamin deficiency and of a discussion of some of the pathologic changes accompanying these deficiency states. There is surprisingly little and in fact almost no information in this report concerning the extent of vitamin deficiency in this country. The absence of such data fairly well summarizes available information on the subject.

An editorial [265] in a recent issue of *The Journal of the American Medical Association* states that, in general, studies of problems relating to the incidence of vitamin deficiency states indicate that deficiency of vitamin D and deficiency of calcium are more frequent than that of any other nutritional element. There also seems to be an increasing amount of both clinical and experimental evidence that deficiency of vitamin B_1 may be more common than previously believed.

The situation in regard to the problem in Great Britain is summarized by a former chief officer of the Ministry of Health, who is quoted as saying that the British are better fed than at any period in their history, that there is no doubt room for improvement and that the diet is overweighed with energy-giving foods instead of protective foods.[266]

The potentiality of a race which consumes a diet rich in protective foods seems to be tremendous. The problems which confront any effort made to secure general distribution of protective foods include not

263. Minot, G. R.: Nutritional Deficiency, Ann. Int. Med. **12**:429-442 (Oct.) 1938.

264. Extent of Vitamin Deficiency in the United States, report of the Committee on Nutritional Problems, American Public Health Association, Am. J. Pub. Health (supp.) **28**:75-80 (Feb.) 1938.

265. Normal Nutrition, editorial, J. A. M. A. **111**:1846 (Nov. 12) 1938.

266. What Is Wrong with the British Diet? Foreign Letters (London), J. A. M. A. **109**:2149 (Dec. 25) 1937.

only those related to nutrition but also those related to economics, finance and racial likes, dislikes and prejudices. As Simmonds [267] has stated, nutrition may now be considered largely a problem of economics and education, and she adds that there is too much of a tendency to discuss nutrition in terms of vitamins, essential amino acids, carotene, thiamin chloride, ascorbic acid, nicotinic acid, dicalcium phosphate, calcium gluconate, units of various vitamins in foods and units of various vitamins needed daily by individuals, whereas to prevent unnecessary confusion the question of a balanced nutrition must be discussed in terms of milk, meat, potatoes, carrots, oranges and cod liver oil. Magee,[268] in discussing this problem at the recent International Physiology Congress in Zurich, emphasized other phases of the subject and then deplored the application of experimental work in the laboratory to mass problems of human nutrition (in India, for example). Leake,[269] in the same discussion, suggested that biochemists might examine the logic of their recommendations in nutrition, particularly in regard to the use of maximal effects on size and weight as the best criteria of biologic excellence.

The diagnosis of vitamin deficiency states presents an important but difficult problem to the clinician. The early general symptoms of nutritional deficiency are vague, as Minot [263] has pointed out, and consist of a sense of fatigue or lack of energy, inefficiency, mental irritability, mild anemia and simple disorders of the digestive tract. The symptoms and signs of deficiency may be referable to the bones; to faulty growth; to the neural, blood-forming and reproductive systems, and to the skin. However, such indefinite symptoms are common in a large variety of diseases. In an effort to obtain objective evidence substantiating a clinical diagnosis of a vitamin deficiency state or in establishing this diagnosis in the absence of specific clinical symptoms, a variety of diagnostic procedures has been suggested. These methods are well summarized in a report of the proceedings of a round table discussion on nutrition and public health at the sixteenth annual conference of the Milbank Memorial Fund [270] and in a series of lectures by Ungley,[271]

267. Simmonds, N.: Recent Research in Nutrition in Relation to Preventive Medicine, J. A. M. A. **111**:1073-1076 (Sept. 17) 1938; The Dietary History and Its Value in Dental and Medical Practice, Am. J. Digest. Dis. & Nutrition **4**: 497-503 (Oct.) 1937.

268. Magee, cited in International Nutritional Problems, editorial, J. A. M. A. **111**:1569 (Oct. 22) 1938.

269. Leake, C. D., cited in International Nutrition Problems, editorial, J. A. M. A. **111**:1569 (Oct. 22) 1938.

270. Nutrition: The Newer Diagnostic Methods, Proceedings of the Round Table on Nutrition and Public Health, New York, Milbank Memorial Fund, 1938.

271. Ungley, C. C.: Some Deficiencies of Nutrition and Their Relation to Disease: I. Origin and Detection of Nutritional Deficiencies, Lancet **1**:875-882 (April 16) 1938.

published in the *Lancet*. In various parts of this review will be found reports from the literature discussing the evaluation of some of these "diagnostic" procedures.

SUMMARIES OF INFORMATION OF IMPORTANCE IN NUTRITION

During the past year there have appeared several books, round table discussions and a series of articles on the vitamins of much value to those interested in the field of nutrition. In *The Journal of the American Medical Association* there has appeared an excellent series of articles on vitamins which have been prepared under the general auspices of the Council on Pharmacy and Chemistry and the Council on Foods. The first article appeared in *The Journal* for Feb. 18, 1938, and the series will be published later in book form. Of value also is a statement appearing in the 1938 edition of New and Nonofficial Remedies as to the claims allowed for the vitamins in preventive medicine and in therapeutics. These claims represent a summary of the present knowledge.

The volume by Williams and Spies [138] entitled "Vitamin B_1 and Its Use in Clinical Medicine" is a valuable discussion of chemical, physiologic and clinical phases of this subject. Of interest particularly to those in the experimental field is a book by Katherine S. Coward,[272] "Biological Standardization of the Vitamins." In this excellent work are discussed vitamins A, B_1, C and D, because they are the only vitamins for which international units and standards have so far been set up.

272. Coward, K. S.: Biological Standardization of the Vitamins, London, Baillière, Tindall & Cox, 1938.

News and Comment

Symposium on Public Health Significance of Virus and Rickettsial Diseases.—The faculty of the Harvard School of Public Health offers a short course of lectures, clinics and demonstrations on virus and rickettsial diseases, with special emphasis on their public health significance, to be held at the school during the week of June 12 to 17, 1939. Lectures on the etiology, epidemiology and methods of control of these diseases, given by members of the faculties and by former students of the Harvard School of Public Health and of the Harvard Medical School, will occupy five mornings. Special clinics and demonstrations will be continued through the week, so that all the members of the symposium can attend. On the last morning a panel discussion will be held on the three main topics presented in the symposium.

The fee for the course will be $25, payable at any time up to June 12. Enrolment, however, should be arranged before June 1, as facilities for many of the clinics and demonstrations are limited. The lectures will be published later in a single volume, which will be sent to each person who registered for the course.

Further information may be had by writing to the secretary of the School of Public Health, 55 Shattuck Street, Boston.

The 1939 Journées médicales de Bruxelles.—The eighteenth session of the Journées médicales de Bruxelles will be held in Liége, Belgium, June 24 to 28, under the presidency of Prof. Ernest Renaux, member of the Académie royale de Médecine.

The scientific program will comprise scheduled authoritative lectures on medical questions, practical demonstrations and operative sessions in the hospitals, and there will be numerous social diversions, as well as excursions to Spa and to the Albert Canal, which has recently been completed.

For information and enrolment, address the secretary, Dr. René Beckers, 141 Rue Belliard, Brussels, Belgium.

CORRECTION

In the article by Dr. Stanley Cobb, "Review of Neuropsychiatry for 1938," in the November issue (ARCH. INT. MED. **62**:883, 1938), in the twelfth line from the bottom of page 884 the word "centimeter" should read "millimeter"; i. e., "White matter has about 200 to 300 mm. of capillary length per cubic millimeter of brain substance, while gray matter has from 600 to 1,000 mm."

Book Reviews

Internships and Residencies in New York City, 1934-1937: Their Place in Medical Education. Report by the New York Committee on the Study of Hospital Internships and Residencies, Jean Alonzo Curran, M.D., Executive Secretary. Price, $2.50. Pp. 492. New York: The Commonwealth Fund, 1938.

The educational opportunities of internships in general have been the subject of much discussion, especially by the Council on Medical Education and Hospitals of the American Medical Association. Stimulated by the new standards for qualification of specialists established by the medical specialty boards, serious consideration is now being given to the educational opportunities provided by the hospital residency.

In the present volume appear the results of investigations of a committee organized by five medical colleges of New York and the New York Academy of Medicine. The factual material was assembled by Dr. Curran and subjected to study by a group of men who for the most part are engaged in medical education. It seems that the city of New York offers more than one sixth of all the internships and residencies of the entire country. Students from all parts of the United States receive training in these positions, and thus these hospitals not only provide a large sampling of the problem of intern residency of the country at large but by example exert a great influence on hospital education everywhere.

Only a few of the many important deductions arrived at by the committee can be mentioned. The preparation of graduates of American and Canadian medical schools is regarded as adequate and, in general, distinctly superior to that provided by foreign schools. With few exceptions men trained abroad fit poorly into the American scheme. Frequently, however, the hospital fails to give new interns adequate instruction regarding their responsibilities and duties, and thus slipshod methods and careless procedure are encouraged. Measured by the quality of medical examinations and by the teaching of technics, much remains to be done to place the internship on a thoroughly satisfactory educational basis. Training in the outpatient department is given the lowest rating.

It was found that the provision of residencies in hospitals distinctly elevates the quality of medical service as well as improves the teaching given to interns and students. The residencies, moreover, are providing opportunities for special training in the basic sciences and other essentials required for the qualification of specialist. This is true, however, only when the appointments are of two years' duration or longer. The standing of residencies in existence should be raised; especially those in surgery need bolstering in quality. Residencies in obstetrics and gynecology enjoy the highest rating, while those in medicine occupy an intermediate position.

The most serious deficiency found in the hospital staffs is a deficit of trained teachers. Little formal effort is made by members of the profession to qualify its members in the art of teaching, and not infrequently the instructing of interns and even of medical students is delegated to physicians who have no understanding of how to organize teaching schedules or to insure the educational progression of their charges. The development of residencies on a truly educational basis offers an opportunity to meet this deficiency. "All thoughtful and forward-looking studies of hospital internships and residencies must arrive at the same conclusion—that their primary and essential function is educational. While they serve a useful purpose in the care of the sick in the modern highly-organized hospital, it is only by this practical, *supervised* experience that the student doctor can be qualified to assume independent responsibility for the care of patients."

This investigation undoubtedly will do much to improve the training of physicians. The work of the committee is to be continued, with the plan of making new surveys from time to time, thus serving as a source of information regarding graduate medical education for those who are responsible for the guidance of students.

The Therapeutic Problem in Bowel Obstruction. By Owen H. Wangensteen. Price, $6. Pp. 360, with 90 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

The publication of this monograph has been made possible by the author's well deserved reception of the Samuel D. Gross prize. In brief, it is a concise but thorough exposition of the more "important aspects of the therapeutic problem in obstruction of the bowel" in the light of the vast investigations and experience of the writer and his co-workers.

The text is divided into three parts: The first section is devoted to a succinct but complete elaboration of the altered physiologic state and the pathologic consequences of obstruction and distention of the bowel, which are clearly demonstrated by the extensive clinical and experimental investigations of the author and his collaborators. On this basis is built the evident rationale and therapeutic efficacy of the administration of saline solution in high obstruction, conservative decompression by suction applied to a duodenal tube, blood transfusion and operation. The second portion of the text consists of a dissertation on the considerations of diagnosis and treatment in cases of obstruction. The criteria for early recognition and differentiation of acute abdominal disorders are lucidly evaluated, and a critical analysis of the therapeutic value of various agents and of the choice of operative procedures is made. The third part is concerned primarily with a classic, textbook description of the accepted facts characterizing the various special types of intestinal obstruction due to congenital atresia, imperforate anus, tumor, stricture, hernia, volvulus, intussusception and other causes.

This compendium may be considered a valuable addition to the modern library of the internist as well as that of the surgeon, not only because it is a thorough exposition of the pathologic physiology and the therapeutic considerations of intestinal obstruction but also because it represents the most recent progress yet made in the management of a condition as perplexing as it is serious. Because in great measure this progress has been due to the important contributions of the author and his co-workers, the book is even more valuable.

Man Against Himself. By Karl A. Menninger. Price, $3.75. Pp. 485. New York: Harcourt Brace and Company, Inc., 1938.

Under this intriguing title there comes from Dr. Menninger's pen another popular work on psychiatry. This time the subject is suicide—thoroughly analyzed, documented with case reports, correlated with "slow suicide" (asceticism) and finally set off in its relations to the "living suicide" type of neurosis. Dr. Menninger writes plausibly; he is clearly a master of exposition in his subject. The inherent motive of self destruction side by side with that of self preservation; the suicide of the banker not because his peculations were discovered but because his mother was hard to him in his childhood; the repressed housewife who refused to go out because she wanted to hurt her husband, whom she really loved but could not resist torturing—all this is exposed and analyzed with admirable clearness. None the less, the reviewer—probably through ignorance—is not convinced at all points. To take one example, the concept of nail biting as a prelude to devouring one's fingers, in other words, self destruction, seems a little far fetched in most cases. Surely many people gnaw their finger nails when nervous just as they twiddle a rubber band or make random scratch marks with a pencil. Does this require an esoteric interpretation? Again, as in the review of Dr. Menninger's previous book, the question is raised as to whether such a treatise is good popular medicine; whether those who need treatment can get it profitably in this way or

will not rather be confused, and whether those who are of reasonably sound mind benefit from material which (to paraphrase Poe) contains much of the wanton, much of the bizarre, something of the terrible and not a little of that which might excite disgust.

Milestones in Medicine. With an introduction by James A. Miller. Price, $2. Pp. 276. New York: D. Appleton-Century Company, Inc., 1938.

This would be a delightful present for one of those many laymen who are interested in medicine or for a young man on the threshold of his premedical course or, for that matter, for a well read practitioner of medicine. Each would find in the volume many interesting new facts.

There are curious facts about the beginnings of psychiatry in Greece in ancient times and even more curious facts about the genes and the ways in which they are now being studied and located in giant chromosomes. Vogel's chapter describing the awful dietary, medical and hygienic conditions which existed on ships in olden times is one of the most interesting in the book. When it is learned how the sailors had to live on stinking water, rotten salt pork and moldy hardtack, it can readily be seen why sometimes half the sailors on a man-of-war died of diarrhea and scurvy.

Tilney gives a brief résumé of what has been learned lately about the intelligence of monkeys and apes. Sigerist writes about the development of the science of medical history. Wayson reviews the history of leprosy and throws light on the questions of why this scourge was so common in Europe in the Middle Ages and why later it disappeared. Doubtless in many cases the diagnosis was wrong. Interesting is Wayson's suggestion that some of the lesions may have been due to ergotism and to the partial starvation which was so common in the Middle Ages. In the last chapter Timme gives a brief but interesting and sane résumé of what is known about the glands of internal secretion.

Men Past Forty. By A. F. Niemoeller, M.A. Pp. 154, with 6 illustrations. New York: Harvest House, 1938.

This little booklet dealing with impotence and rejuvenation in fairly simple, easy language is obviously intended for the layman, although it may be read with profit by the average practitioner. The reader is adequately admonished to consult only reputable physicians and specialists and to avoid the quack preparations and appliances advertised in sensational magazines. The author is inclined to agree with Steckel and his disciples that psychic impotence greatly predominates over the so-called secondary organic or physiologic form. This point of view undoubtedly will be shared by the majority of the members of the medical profession. The medical treatment and the psychotherapeusis of the condition are outlined. The aphrodisiac yohimbine alone or in combination with various other preparations is favored. The author also lists a number of the foreign and domestic preparations of aphrodisiac and organotherapeutic nature and their manufacturers. The organotherapy and surgical treatment of rejuvenation are discussed with proper conservatism. The volume closes with a brief chapter on the menopause in men and includes Dr. Lorand's "twelve commandments" for avoiding premature old age, which are largely injunctions for hygienic living.

A Diabetic Manual. By Elliott P. Joslin. Sixth edition, thoroughly revised. Price, $2. Pp. 219, with 49 illustrations. Philadelphia: Lea & Febiger, 1937.

Protamine zinc insulin has opened another door to the diabetic patient. In the sixth edition of the "Diabetic Manual" Dr. Joslin makes available to both physician and patient the most recent methods of using this long-acting insulin intelligently and effectively. The advantages and disadvantages of the use of protamine zinc insulin as they appear at present are given in detail.

The chapter on diabetic children is most interesting and dramatic. Here are emphasized the necessity for education of the child and the importance of yearly

adjustments in his diet to take care of normal growth as well as activity. Helpful suggestions and instructive tables relative to dietary calculations and the planning of the menu form an important part of this valuable book.

The book covers the subject of diabetes well and gives all the essential information necessary for the intellligent care of the patient. Education of the patient is the keynote of this manual.

Pneumonia and Serum Therapy. By Frederick T. Lord and Roderick Heffron. Revised edition. Price, $1. Pp. 148, with 10 illustrations and 10 tables. New York: The Commonwealth Fund, 1938.

This little book is an ideal summary of the recent developments in the typing of pneumococci and in serum therapy. A vast amount of information scattered throughout the literature has been assembled, with practical directions about procedure. The tables and charts are particularly valuable, and the physician has ample material from which to draw his own conclusions as to whether serum therapy is indicated in an individual case.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung, Volume 140. Edited by Prof. Dr. Eberhard Koch. Price, 15 marks. Pp. 320. Dresden: Theodor Steinkopff, 1937.

In this well printed and profusely illustrated volume are reported the papers read at the 1937 meeting of the German society for the study of the circulation. The material is miscellaneous and does not lend itself to review in brief space. There are many interesting articles by authorities on various aspects of the circulation.

Anniversary Volume: Scientific Contributions in Honor of Joseph Hersey Pratt on His Sixty-Fifth Birthday. By His Friends. Price, $7. Pp. 983. Lancaster, Pa.: Lancaster Press, Inc., 1937.

This *Festschrift,* as appears from the title, contains a collection of papers by various authors. The subjects, like Dr. Pratt's own activity, range over the entire field of the science, practice, history and teaching of medicine. The contributors number one hundred and twenty. The separate papers have already been published in the *Annals of Internal Medicine.*

Traitement chirurgical du cancer du côlon pelvien. By Pierre Bertrand and E. Corajod. Price, 30 francs. Pp. 208, with 36 illustrations. Paris: Masson & Cie, 1936.

This little volume follows the French manner of dealing in monographic style with a narrow subject. The work is really an enlarged textbook article and covers the subject adequately, but it adds nothing fundamental. The illustrations are poor.

Nuevos estudios sobre los neumotórax espontáneos. By Mariano R. Castex and Egidio S. Mazzei. Pp. 164. Buenos Aires: "El Ateneo," 1937.

This small book deals with spontaneous pneumothorax and its chief causes. The authors differentiate between blebs, bullae, recurrent pneumothorax and tuberculosis as causative agents. The book is well worth while for those who are interested in the subject and can read Spanish.

Sindrome adiposo genital. By Luis Viamonte Cuervo. Pp. 62, with 30 illustrations. Habana: Seoane, Fernandez y Cia, 1937.

This is a brief presentation of a quite common syndrome. The work is largely a report of a series of cases plus a fairly extensive review of the literature, for the most part of the Latin countries.